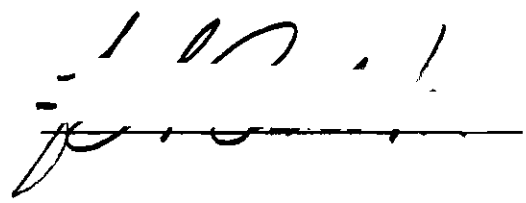
In presenting the dissertation as a partial fulfillment of the requirements for an advanced degree from the Georgia Institute of Technology, I agree that the Library of the Institute shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to copy from, or to publish from, this dissertation may be granted by the professor under whose direction it was written, or, in his absence, by the Dean of the Graduate Division when such copying or publication is solely for scholarly purposes and does not involve potential financial gain. It is understood that any copying from, or publication of, this dissertation which involves potential financial gain will not be allowed without written permission.



7/25/68

THE STRUCTURES OF VIOCIDIC ACID, 2-(2,3-DICHLORO-2-PYRROLIN-1-YL)-1-PYRROLINE, AND VICANICIN

A THESIS

Presented to

The Faculty of the Graduate Division

by

Fred LeRoy Suddath, Jr.

In Partial Fulfillment

of the Requirements of the Degree

Doctor of Philosophy

in the School of Chemistry

Georgia Institute of Technology

February, 1970

THE STRUCTURES OF VIOCIDIC ACID,

2-(2,3-DICHLORO-2-PYRROLIN-1-YL)-1-PYRROLINE, AND VICANICIN

Approved:

Chairman

Date approved by Chairman: February 19, 1970

The chymists are a strange class of mortals impelled by an almost insane impulse to seek their pleasure among smoke and vapour, soot and flame, poisons and poverty, yet among all these evils I seem to live so sweetly, that may I die if I would change places with the Persian King.

-Johann Joachim Becher
Acta Laboratorii Chymica Monacensis, seu Physica Subterranea [1669]

ACKNOWLEDGMENTS

The author is grateful to Dr. John R. Dyer for his interest and invaluable guidance during the entire period of this research and in the preparation of this thesis. For reading and criticizing this thesis and for his interest in and patient guidance of the X-ray diffraction studies, the author wishes to thank Dr. J. Aaron Bertrand. The author also wishes to thank Dr. Drury S. Caine, III for reading and criticizing this thesis. Financial assistance provided by the National Science Foundation and the Rayonier Corporation is gratefully acknowledged.

The author wishes to thank Mr. James A. Kelley and Mr. Charles E. Kirkwood for their assistance during the X-ray diffraction studies. The author also wishes to thank the personnel at the Rich Electronic Computer Center for their cooperation and assistance during the calculations associated with the X-ray structure determinations.

For their assistance and encouragement the author is deeply indebted to his family and especially to his wife, for without her understanding, patience and encouragement this research would have been impossible.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

LIST OF FIGURES

GLOSSARY OF ABBREVIATIONS

ct	column temperature
DCC	dicyclohexylcarbodiimide
DMSO	dimethylsulfoxide
d	doublet
emd	exact mass determination
glpc	gas liquid partition chromatography
ir	infrared
lpr	linear programming rate
glpc/ms	mass spectrum obtained from gas chromatography effluent
M^+	molecular ion
m	multiplet
nfr	nitrogen flow rate
nmr	nuclear magnetic resonance
psig	pounds per square inch guage
q	quartet
R_t	retention time
s	singlet
DSS	sodium 2,2-dimethyl-2-silapentane-5-sulfonate
TMS	tetramethylsilane
tlc	thin layer chromatography
TFA	trifluroacetic acid
TFAA	trifluroaetic anhydride

t	triplet
uv	ultraviolet

SUMMARY

Viomycin is an antibiotic composed of the amino acids *L*-serine, *L*-α,β-diaminopropionic acid, *L*-β-lysine, and viomycidine. From the partial acid hydrolysate of viomycin it is possible to isolate a compound more basic than viomycidine that can be crystallized as the dihydrobromide salt. Precession photographs revealed the space group as $P2_12_12_1$ and the unit cell dimensions a = 8.17(2)Å, b = 12.22(2)Å, and c = 15.34(2)Å. These dimensions were within experimental error of the dimensions reported for viocidic acid by Johnson, *et al.* The structure was redetermined since there was some doubt as to the structure proposed for viocidic acid. Solution of the structure by a conventional application of the heavy atom method revealed the structure to be 2,5,8,10-tetraaza-9-iminotricyclo[5.3.1.$0^{4,11}$]undecane-6-carboxylic acid, identical with that proposed for viocidic acid. The structure refined to an R_1 value of 0.0901 using 1031 unique reflections. A mechanism is proposed to explain the genesis of viocidic acid from a peptide known to be present in the hydrolysis medium.

The product reported for the reaction of 2-pyrrolidinone treated sucessively with hydrogen chloride, phosphorous pentachloride, and strong base is 2-chloro-Δ^1-pyrroline. Preliminary spectroscopic data indicated the reported structure was incorrect. When further spectroscopic investigations and preliminary chemical test were not definitive, an effort was undertaken to obtain crystals suitable for X-ray

investigation. The compound formed stable mineral acid salts, and the hydrobromide salt was obtained crystalline. Precession photographs showed the crystal to be monoclinic of space group $P2_1/c$. From diffractometer data unit cell dimensions of a = 9.193(2)Å, b = 21.901(10) Å, c = 9.428(3)Å, and β = 138.166(20)° were obtained. A total of 2197 reflections were collected and averaged to give 1042 unique reflections. The structure determined by conventional application of the heavy atom method was (*E*)-2,3-dichloro-1-(2-pyrrolidinylidine)-2-pyrrolinium bromide and refined to an R_2 value of 0.0492 based on 604 nonzero unique reflections. Spectroscopic data indicate the structure of the free base to be 2-(2,3-dichloro-2-pyrrolin-1-yl)-1-pyrroline.

Examination of the lichens *Teloschistes flavicans, Teloschistes flavicans norm.,* and *Teloschistes flavicans v. minor Crombie* by several workers resulted in the isolation of a colorless substance that showed mp 240-245°. Seshadri, *et al.* in 1962 named the colorless substance vicanicin, and reported the structure to be 2,4-dichloro-3-hydroxy-7-methoxy-1,5,8-trimethyldepsidone. In 1967 Balthis proposed a new structure for vicanicin based on spectroscopic data as 2,4-dichloro-3-hydroxy-7-methoxy-1,5,6,8-tetramethyldepsidone. In 1968 Baillie proposed a new structure for vicanicin based on biogenitic arguments as 2,6-dichloro-3-hydroxy-7-methoxy-1,4,5,8-tetramethyldepsidone. A careful examination of the earlier degradative studies indicated several ambiguities that require further investigation. The structure of the two products obtained when methyl *O*-methylvicanicate is oxidized

were shown to be methyl 5-chloro-3,6-dimethyl-2-hydroxy-4-methoxybenzoate and 3-chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone by synthesis. The hydroxyl group in vicanicin was shown to be in the A ring by conversion of vicanicin to *O*-ethylvicanicin and degradation to methyl 5-chloro-3,6-dimethyl-4-ethoxy-2-hydroxybenzoate. Consideration of the probable mechanism of the oxidative hydrolysis of methyl *O*-methylvicanicate lead to 2,7-dichloro-3-hydroxy-6-methoxy-1,4,5,8-tetramethyldepsidone as the structure of vicanicin.

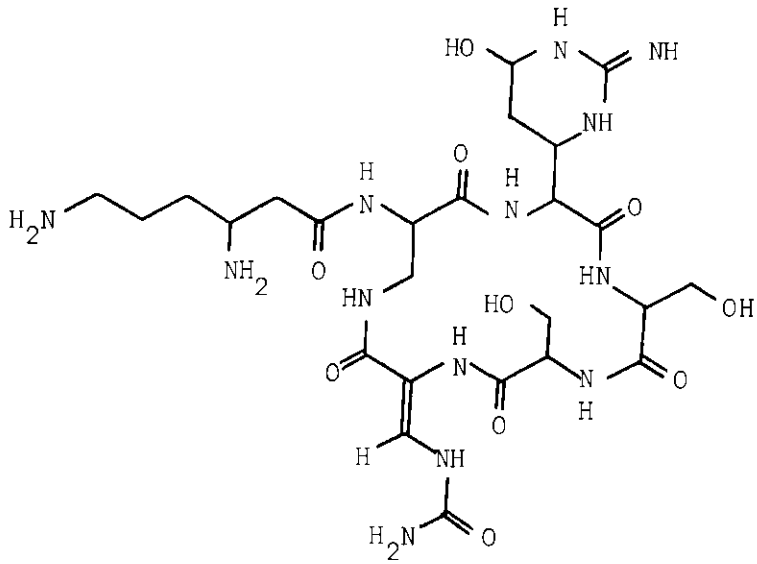
CHAPTER I

INTRODUCTION

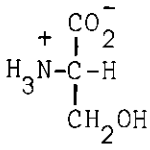
The Crystal Structure of Viocidic Acid

Viomycin is a broad spectrum antibiotic that is particularly effective against *Mycobacterium tuberculosis*.[1] The antibiotic was first reported in 1951 simultaneously by Charles Pfizer and Company[1] and Park, Davis and Company[2] from cultures of *Streptomyces puniceus* and *Streptomyces floridae*. Later clinical studies showed that kidney damage, vestibular dysfunction, electrolyte imbalance, and hypersensitivity resulted from its extended use.[3] In spite of these toxic reactions, viomycin is still used clinically in cases where the tuberculosis microorganism has become resistant to streptomycin.

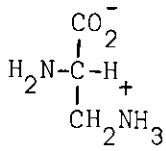
Elucidation of the structure of viomycin has proceeded in several laboratories in order to ultimately study the structure-biological activity relationships. Extensive studies of the complete degradation of viomycin and the most recently proposed structure for viomycin (1) are reported elsewhere.[4-8] These studies have shown that viomycin is a peptide composed of the amino acids *L*-serine (2), *L*-α,β-diaminopropionic acid (3), *L*-β-lysine (4), and viomycidine (5) in addition to urea, carbon dioxide, and ammonia. The recent single crystal X-ray diffraction analysis of viomycidine hydrobromide revealed 2,4,6-triaza-3-iminobicyclo [3.2.1]octane-7-carboxylic acid to be the correct structure of viomycidine.[9]



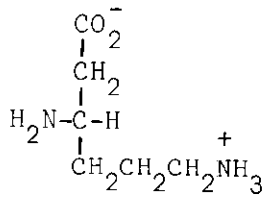
1



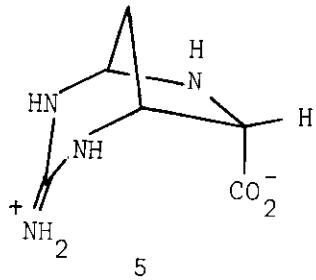
2



3

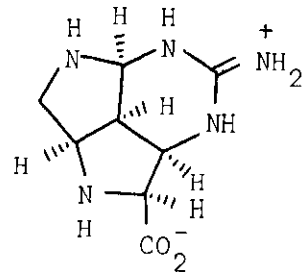


4



5

In addition to viomycidine, another guanidino compound was reported to occur in the total acid hydrolysate of viomycin. A quantity of this material, referred to by Streetman as Peptide III, was purified and converted to the hydrobromide salt.[6] Peptide III dihydrobromide was crystallized from acetone-water to give colorless needles. The unit cell dimensions of Peptide III dihydrobromide obtained from precession photographs were within experimental error of the dimensions reported by Johnson and co-workers for the compound viocidic acid.[10] However, the molecular formula reported by Johnson ($C_8H_{13}N_5O_2 \cdot 2HBr \cdot 3H_2O$) for viocidic acid (6) did not agree with the analytical data obtained by Streetman for Peptide III.[6]



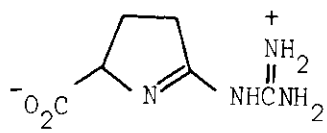
6

The molecular formula for Peptide III that best fit the analytical data was $C_9H_{15}N_5O_3 \cdot 2HBr \cdot 1H_2O$, which would be quite reasonable if two of the water oxygen atoms in crystals of viocidic acid had been incorrectly assigned. Unequivocal assignment of atomic number to the light atoms (*C,N,O*) in a structure such as 6 on the basis of diffraction data is difficult. It would be possible to assign atomic numbers on the

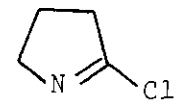
basis of geometrical evidence (the nitrogen and carbon atoms of the guanidino group are in the same plane). However, in the structure proposed for viocidic acid, the positions of two of the five nitrogens atoms were not fixed by chemical or geometrical arguments. At the time structure 6 was reported there was little chemical evidence that would substantiate 6 as being a chemically logical structure for Peptide III. Normally a structure determined by X-ray diffraction methods would be quite conclusive. However, since bond lengths and angles were not reported for viocidic acid, and because the factors stated above were seemingly in conflict with the reported structure, it was decided to redetermine the structure of viocidic acid.

The Structure of 2-(2,3-Dichloro-2-Pyrrolin-1-yl)-1-Pyrroline

Acid hydrolysis of the antibiotic viomycin yields among other amino acids, viomycidine (5).[6,7] Another structure, 2-guanidino-Δ^1-pyrroline-5-carboxylic acid (7), had been proposed for this guanidino amino acid prior to the single crystal X-ray analysis of the hydrobromide salt.[9] During studies directed toward the synthesis of 7, it was desirable to obtain 2-chloro-Δ^1-pyrroline (8). Tafel and Wassmuth[11]



7



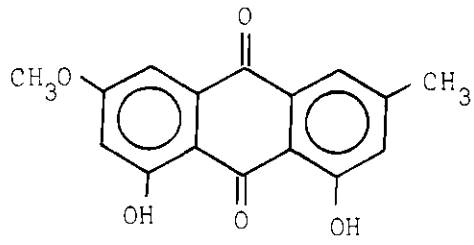
8

reported the synthesis of 8 from 2-pyrrolidinone in 1907. Baillie[12] repeated their work and obtained an unstable crystalline compound that analyzed correctly for 8 (C_4H_6NCl). The material was difficult to purify by crystallization, but the crude crystals obtained agreed in melting point with that reported earlier (50-51° corr). The 2-chloro-Δ^1-pyrroline was expected to be very reactive toward nucleophilic reagents since it is analogous to an acid chloride. When 8 was treated with aqueous ammonia or aqueous guanidine, none of the expected products was obtained. Even more surprising, unreacted 8 could be recovered from the reaction mixture. Since this chemical behaviour seemed inconsistent with the proposed structure, an investigation of the spectroscopic properties of 8 was made. The nmr spectrum of 8 showed absorptions for five different types of protons, which was inconsistent with the structure proposed. The mass spectrum of 8 showed a molecular ion at *m/e* 204. A determination of the exact mass of this ion (*m/e* 204.029) dictated $C_8H_{10}N_2Cl_2$ (calcd *m/e* 204.022) as the molecular formula. This is equal to twice the molecular formula reported by Tafel and Wassmuth less two hydrogens. Spectroscopic data and preliminary chemical investigations were not definitive; therefore it was decided to further investigate the chemistry of 8 and to obtain crystals suitable for X-ray investigation.

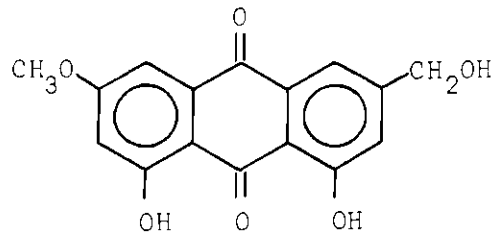
The Structure of Vicanicin

The first examination of the lichen *Teloschistes flavicans* by Zopf in 1905[13] resulted in the isolation of parietin, referred to by Zopf as physcion, (4,5-dihydroxy-7-methoxy-2-methylanthraquinone) (9)

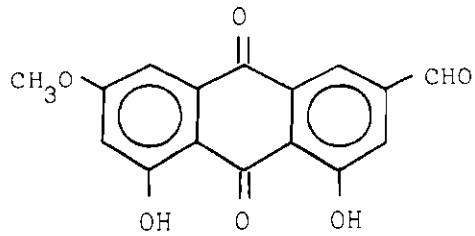
and a colorless substance, mp 240-245°. In 1949 Seshadri and Subramanian reported the isolation of parietin, teloschistin (4,5-dihydroxy-2-hydroxymethyl-7-methoxyanthraquinone) (10), and a colorless substance, mp 240-245°, from an Indian sample of *Teloschistes flavicans Norm.*[14] A sample of the same lichen, collected in 1955, contained fallacinal (2-formyl-4,5-dihydroxy-7-methoxyanthraquinone) (11) instead of teloschistin and the colorless substance mp 240-245°.[15] Thus there were variations in the composition of the anthraquinone pigments, but the colorless substance seems to occur in all the lichen samples.



9



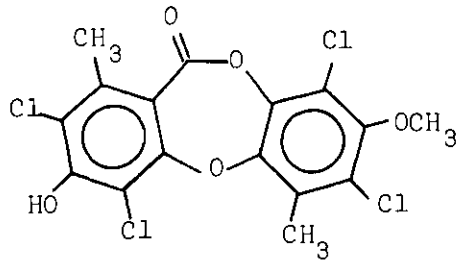
10



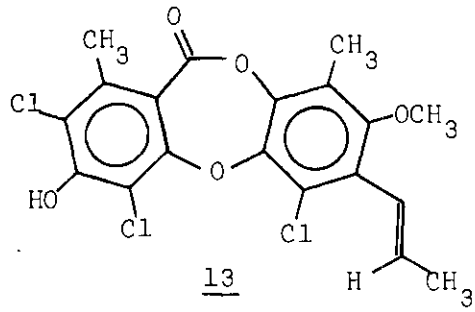
11

In 1962 Seshadri, *et al.* reported the first work directed toward the identification of the colorless substance, which they named vicanicin.[16] Vicanicin was originally isolated in a small amount (*ca.* 0.1%) from the alkali-insoluble fraction of the petroleum ether extract of the lichen. Later, using column chromatography on magnesium carbonate,

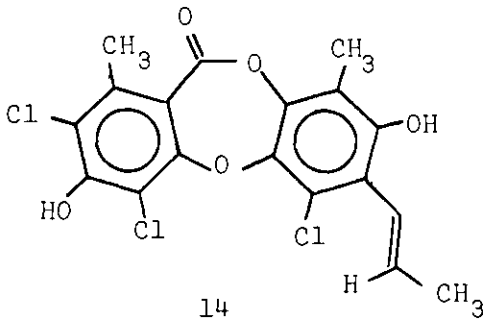
vicanicin was isolated pure and in better yield (*ca.* 1%). Vicanicin was crystallized from boiling benzene as colorless crystals, mp 248-250°. The analytical data agreed with the molecular formula $C_{17}H_{14}O_5Cl_2$. The compound was shown to contain one methoxyl group by the Zeisel method (found, 1.06) and three *C*-methyl groups by the Kuhn-Roth method (found, 2.76).[16] Vicanicin contained a free hydroxyl group since it formed a monoacetate, mp 213-214°, by acetylation with acetic anhydride, and a monobenzoate, mp 190-191°, with benzoyl chloride and pyridine. The free hydroxyl group was phenolic in nature since it readily underwent methylation and ethylation with the appropriate alkyl iodide and potassium carbonate, yielding *O*-methylvicanicin, mp 193-194°, and *O*-ethylvicanicin, mp 185-186°. It was concluded that vicanicin contained a lactone ring since treatment of *O*-methylvicanicin with 2*N* sodium hydroxide in dioxane followed by acidification yielded a hydroxy acid, *O*-methylvicanicic acid, mp 212-218°. When *O*-methylvicanicin was heated under reflux with methanolic sodium methoxide, the product obtained, methyl-*O*-methylvicanicate, mp 155-156°, still contained a free hydroxyl group that could be methylated to give a neutral compound, methyl-*O*,*O'*-dimethylvicanicate, mp 97-98°. The uv spectrum of vicanicin was compared to those of diploicin (12),[17] nidulin (13),[18] and nornidulin (14),[18] and they were shown to be similar. These compounds, 12, 13, and 14 are all chlorodepsidones and the numbering system for the nucleus is shown by structure 15. Since four of the five oxygen atoms in vicanicin were accounted for by the free hydroxyl, methoxyl, and lactone function, the fifth oxygen was assigned to an inert diphenyl



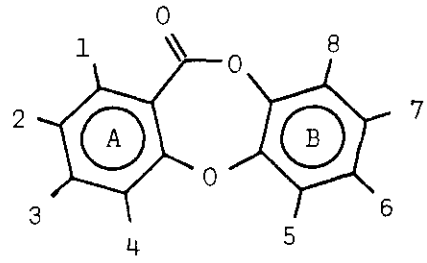
12



13

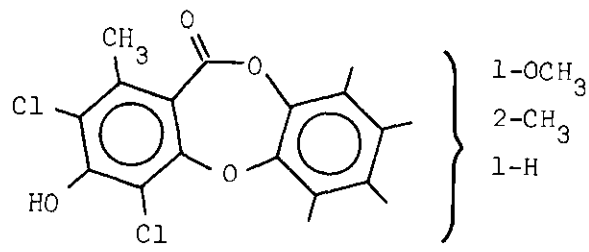


14



15

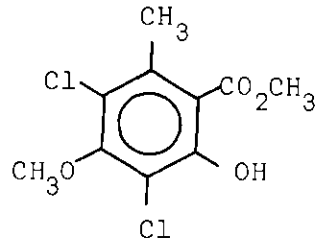
ether linkage. Dean, *et al.*[18] reported that the characteristic uv spectra of the chlorodepsidones were associated with ring *A*; therefore a partial structure was assigned to vicanicin (16)[16] assuming that the *A* ring was identical to those of 12, 13, and 14.



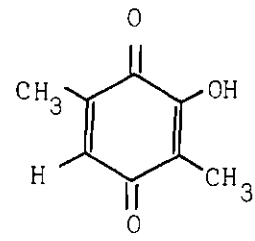
16

When methyl-*O*-methylvicanicate was dissolved in acetic acid and treated with concentrated nitric acid, two products were obtained.

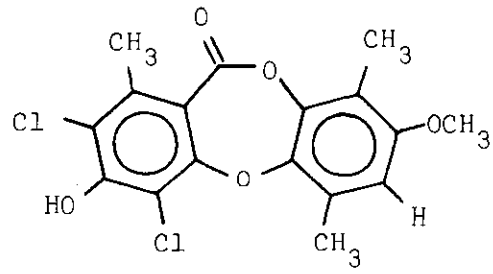
A phenol reported to be methyl 3,5-dichloroeverninate (17)[19] was isolated as a crystalline solid, mp 76-78°. A quinone was present in the sodium bicarbonate-soluble fraction. The quinone was reported to be 2-hydroxy-3,6-dimethyl-*p*-benzoquinone (18)[20] by comparison of their uv spectra in a buffer solution. These data lead Seshadri, *et al.* to extend the partial structure 16 to a complete structure for vicanicin (2,4-dichloro-3-hydroxy-7-methoxy-1,5,8-trimethyldepsidone) (19).



17



18



19

In 1965 investigators[21] in these laboratories obtained a quantity of a lichen gathered from volcanic rocks in the Ascension Islands. The lichen, identified as *Teloschistes flavicans v. minor Crombie*,[22] was much smaller than the samples of *Teloschistes flavicans* previously investigated, probably due to the unusual habitat of the Ascension Islands. Extraction of 1,426 g of the lichen with chloroform yielded, after chromatography, 8.08 g (*ca.* 0.6%) of gold-colored material and

8.75 g (*ca.* 0.6%) of pale yellow material. The gold-colored material was recrystallized twice from glacial acetic acid to yield gold-colored crystals, mp 207-208°. The gold-colored compound was identified as parietin (10) based on melting point, spectral data, and the diacetyl derivative.[23] The pale yellow material was recrystallized twice from benzene to give colorless crystals, mp 239-240°.[23]

Based on the method of isolation and similarity in mp it was considered possible that compound 20 was vicanicin. The likelihood that the structure proposed for vicanicin was the correct structure for compound 20 was eliminated when the nmr spectrum of 20 clearly showed four *C*-methyl group absorptions and no aromatic proton absorption, as would have been expected for structure 19. The elemental analyses of compound 20 were satisfactory for the formula $C_{18}H_{16}O_5Cl_2$, which is one carbon and two hydrogens more than the formula reported for vicanicin. The mass spectrum of compound 20 also supported the formula $C_{18}H_{16}O_5Cl_2$, mw = 383.31. The ratios of ion intensities in the region of the molecular ion [*m/e* 382(23%), 384(16%), and 386(3%)] were in agreement with the expected ratios for a compound containing two chlorine atoms (obsd 1.00:0.69:0.13; calcd 1.00:0.653:0.106).[24] These data showed that 20 was not represented correctly by the structure proposed for vicanicin (19). However, the possibility still existed that 20 was identical with vicanicin but the structure proposed for vicanicin was incorrect.

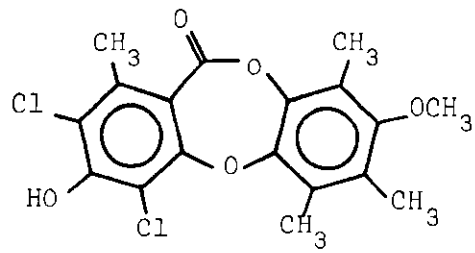
Preparation of derivatives and degradation of compound 20 were carried out to compare the results with those reported for vicanicin.

The method of preparing acetylvicanicin was followed using compound 20 and yielded a colorless crystalline solid, mp 210-211°.[23] The elemental analyses were satisfactory for $C_{20}H_{18}O_6Cl_2$. The nmr spectrum was satisfactory for the addition of one acetyl group. The procedure for preparing *O*-methylvicanicin was repeated using compound 20, and the product, obtained in 70 per cent yield, was a colorless crystalline solid, mp 192-193°.[23] Elemental analyses supported the formula $C_{19}H_{18}O_5Cl_2$. The mass and nmr spectra were consistent with the addition of one *O*-methyl group to 20. Compound 20 was converted to the *O*-methyl derivative, and this product was treated with methanolic sodium methoxide to give a colorless crystalline solid in 70 per cent yield, mp 154-156°. The analytical data, nmr spectrum, and mass spectrum were consistent with methanolisis of a lactone and supported the formula $C_{20}H_{22}O_6Cl_2$.[23] The nitric acid oxidation reported for vicanicin was repeated using 20, and the phenolic fragment obtained showed mp 76-78°.[23] A comparison of the melting points of derivatives and degradation products obtained from compound 20 with those reported for vicanicin is shown in Table 1. From the data in Table 1 it was concluded that compound 20 and vicanicin were identical, but that the structure reported for vicanicin was incorrect.

Balthis[23] proposed a revised structure for vicanicin (21) based on analytical data, derivatives, and spectral evidence. However, when Baillie[25] re-examined the nitric acid oxidation of methyl-*O*-methylvicanicate, he was able to obtain the quinone fragment in crystalline form, mp 126-128°. The behavior of this material by tlc was different

Table 1. Comparison of Vicanicin and Compound 20

Derivative	Vicanicin, mp[16]	Compound 20, mp
Vicanicin	240-245°	239-240°
	248-250°[14]	
Acetyl-	213-214°	210-211°
O-methyl-	193-194°	192-193°
O-ethyl-	185-186°	185-186.5°
methyl-*O*-methyl-	155-156°	154-156°
Phenol from oxidation of methyl-		
O-methyl-	76-78°	76-78°
methyl-*O*,*O*'-dimethyl-	96-97°	94-97°

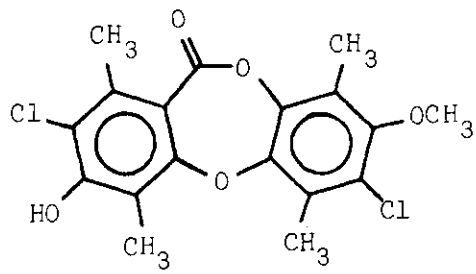


21

from that of hydroxytrimethyl-*p*-benzoquinone (the quinone expected from the structure proposed by Balthis[23]). A complete investigation of this quinone was undertaken by Baillie. The mass spectrum and analytical

data were consistent with the formula $C_8H_7O_3Cl$. The nmr spectrum in deuterochloroform showed absorptions at 7.77 ($-CH_3$,s), 7.98 ($-CH_3$, s), and 3.00τ (-OH). The structure of this quinone was proved by the unambiguous synthesis of 3-chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone, and a comparison of nmr and mass spectra showed them to be identical. The natural and synthetic material showed identical behavior by tlc in several solvent systems, and the mmp was not depressed, mp 127-128°.[25] However, structure proof of the quinone fragment did not prove the structure of the *B* ring of vicanicin since the quinone could arise from either of two structures (interchange of substituents at *C*-6 and *C*-7).

From the oxidation Baillie also isolated the phenolic fragment from ring *A*. The nmr and mass spectra showed the compound contained two *C*-methyl groups, two *O*-methyl groups, one chlorine and one acidic proton. These data were consistent with the formula $C_{11}H_{13}ClO_4$. One of the *C*-methyl groups was assigned the *C*-1 position, *ortho* to the carbonyl group, since the nmr spectrum showed an absorption at 7.40τ corresponding to a deshielded *C*-methyl group. The location of the other substituents was not apparent from the data. Baillie attempted to resolve these and other ambiguities by single crystal X-ray diffraction. The iodoacetyl derivative of vicanicin was prepared and obtained as apparently single crystals. After collection of the X-ray data it was not possible to find suitable locations for the iodine atoms, and it was then assumed that the crystals had been twinned. From the chemical data available and biogenitic arguments, Baillie, *et al.*[26] proposed a new structure for vicanicin (22).



22

When structure 22 was proposed for vicanicin, it was recognized that several of the structural features were presented solely on the basis of analogies with similar compounds. Conclusive proof of the location of the free hydroxyl group was not available. Most of the earlier chemistry had been done on *O*-methylvicanicin, and the location of the free hydroxyl group had been assigned to ring *A*, rather than ring *B*, on the basis of analogies presented by Dean, *et al.*[18] The interchange of substituents at positions *C*-6 and *C*-7 of 22 would satisfy all the accumulated data. The location of the *C*-2, *C*-3, and *C*-4 substituents in ring *A* were assigned on the basis of biogenetic arguments and comparison of the spectrum with those of 12, 13, and 14.[18] It was for these reasons that more conclusive evidence for the structure 22 was required.

The purpose of additional research was to resolve these ambiguities by synthetic and further degradative studies and to obtain crystalline derivatives of vicanicin suitable for X-ray analysis.

CHAPTER II

EXPERIMENTAL

Apparatus and Techniques

Spectra

Nuclear magnetic resonance spectra (60 MHz) were obtained using Varian Associates Models A-60A or A-60D spectrometers equipped with spin-decoupler and variable temperature attachments. Nuclear magnetic resonance spectra (100 MHz) were obtained using a Jeolco Model 4H-100 spectrometer operated in the field sweep mode and equipped with a variable temperature controller. Spin decoupling experiments were performed using the Jeolco instrument in the frequence sweep mode. Chemical shift values are reported in τ units ($\tau = 10-\delta$). The internal standards used were TMS or DDS.

All mass spectral data were obtained using a Varian Associates Model M-66 mass spectrometer. This mass spectrometer was interfaced with a Varian Aerograph Model 200 gas chromatograph. Exact mass determinations were obtained by linear interpolation between ions of an internal standard of known mass.

Infrared spectra were obtained using a Perkin-Elmer Model 457 or 237B spectrophotometer. The spectra of liquids were obtained as films formed between two sodium chloride plates. The spectra of solids were obtained from potassium bromide pellets pressed at 2500 psig or as chloroform solutions in 0.1 mm sodium chloride cells.

Ultraviolet spectra were obtained using a Cary Model 14 spectrophotometer. Matched 1.0 cm quartz cells equipped with matched 9 mm quartz plugs were used. The spectra were recorded as solutions in 95 per cent ethyl alcohol (U.S.I. pure ethyl alcohol, U.S.P. grade) or *n*-hexane (Fisher H-334 Certified A.C.S. Spectroanalyzed *n*-hexane, Lot. 775206).

Chromatography

Gas chromatography was performed using a Varian Aerograph Model 1740 gas chromatograph equipped with dual hydrogen flame detectors and a linear temperature programmer. Stainless steel columns were prepared with solid supports and liquid phases obtained from Applied Science Laboratories. Two columns were used for most of the separations: (1) a 1/8" x 5', 3% SE-30, on acid-washed, and silinized chromosorb W and (2) 1/8" x 12', 3% OV-17, on acid-washed and silinized chromosorb W. The column temperature, linear programming rate, nitrogen carrier gas flow rate, and the retention time are given for each example. The relative peak areas were measured using a Gelman Instruments Co. planimeter.

Thin layer chromatography was used for qualitative analysis, and the plates were prepared as described previously.[6] Ninhydrin spray reagent was used as described previously[27] for visualization of spots corresponding to amino acids. Iodine vapor and uv lamps were also used for visualization of spots on tlc plates.

Alumina chromatography columns were prepared by slowly pouring the indicated amount of the acid-washed alumina (Merck 71695) into a

cylindrical column that was already half filled with the indicated solvent. The column had a coarse, fritted glass disc at the bottom and was packed by draining the excess solvent, accompanied by vibration, until the adsorbent was firm. The packed dimensions are given in the text.

Silicic acid chromatography columns were prepared by mixing the indicated amount of silicic acid (Unisil 200-325 mesh, Clarkson Chemical Co.) with chloroform. The slurry was slowly poured into a cylindrical column that had a coarse, fritted disc at the bottom. The column was packed by draining the excess chloroform, accompanied by stirring, followed by vibration until the adsorbent was firm. The packed dimensions are given in the text.

X-ray Data

Preliminary orientation pictures were obtained using a Buerger precession camera (Charles Supper Co.) fitted with a Polaroid XR-7 film cassett. The crystal to film distance was 60 mm. Zirconium filtered Mo Kα radiation generated by a Picker full wave X-ray generator was used for the orientation photographs. The intensity data collected by photographic methods were obtained by using Illford Industrial G X-ray film (5" x 7", cut to fit a film envelope, *ca.* 5" x 6 3/8") in an equi-inclination Weissenberg camera (Nonius, Delft, Holland). Nickel filtered Cu Kα radiation generated by a Philips full wave X-ray generator was used to collect the intensity data.

A Picker automated four-circle diffractometer equipped with a Picker full wave X-ray generator was used to collect the diffractometer

data. Zirconium filtered Mo Kα radiation was used for data collection. The diffractometer was automated by a direct relay to an IBM 026 key punch, through which information was conveyed to and from the diffractometer by punched cards. A NaI (Tl) scintillation detector was used to count the diffracted radiation.

A Univac 1108 computer was used extensively in the structure determinations. An off-line Calcomp plotter, California Computer Products, Inc., was used to plot the molecular structures shown in the text.

Miscellaneous

Unless otherwise stated, all concentrations and evaporations were performed using a modified, all glass Rinco (Model VE-1000A) rotory evaporator at water aspirator vacuum and steam bath temperature or at oil pump vacuum and water bath temperatures of 50° or less. Drying of solutions and extracts in organic solvents was accomplished, unless otherwise stated, by the addition of anhydrous sodium sulfate or molecular sieves (Linde 3 or 4 Å, 1/16° pellets). The drying agent was removed by gravity filtration and washed thoroughly with several fresh portions of solvent.

All melting points were obtained using a Köfler hot stage and are corrected. Microanalyses were performed by Bernhardt Laboratories (Mülheim, West Germany).

Anhydrous ether (Fisher reagent E-138) was stored over sodium ribbon. All solvents were redistilled and stored as described elsewhere.[28] The *n*-butyllithium was obtained from Alfa Inorganics, Inc.

as a 21.1 wt per cent solution in hexane (*ca.* 2.25*M*) and used as received. Diazomethane was generated from EXR-101 obtained from E. I. Dupont Nemours, Inc. (Gibbstown, New Jersey), by the method described elsewhere.[29] Diazoethane was prepared by the method described for diazomethane, but bis-(*N*-ethyl-*N*-nitroso)terephthalamide prepared by standard methods[30] was substituted for EXR-101.

Throughout the experimental text the solvents high, medium, and low boiling petroleum ether refer to solvents purified as follows: High boiling petroleum ether was Practical Grade Eastman Ligroin (density 0.69-0.71/20°) that was glass distilled and the fraction boiling at 105°-115° (uncorrected) was collected and stored over sodium ribbon; medium boiling petroleum ether was Practical Grade Eastman Ligroin (density 0.68-0.70/20°) that was glass distilled and the fraction boiling at 66-75° (uncorrected) was collected; low boiling petroleum ether was Practical Grade Eastman Ligroin (density 0.63-0.64/20°, bp 35-60°) stored as received over sodium ribbon.

In the tables and text, numbers in parentheses that follow numerical data represent the estimated standard deviation in the last significant digit.

The atom numbering system used in the Figures corresponds to the order in which the atoms were located and does not correspond to any chemical convention.

Viocidic Acid

Description and Mounting of the Crystal

A solution of viocidic acid dihydrobromide in acetone-water (*ca.* 1:1) was slowly cooled, and clear colorless crystals were obtained (mp 200-205° dec).[6] From these crystals a suitable needle shaped crystal was chosen with dimensions *ca.* 0.5 × 0.25 × 0.25 mm. A section of the crystal perpendicular to the needle axis was approximately a regular hexagon. The density of a crystal was obtained by mixing carbon tetrachloride and bromoethane until a solution was found in which the crystal would remain stationary. The density of this solution was then measured at 20° and was found to be 1.854(2) g cm^{-3}.

The crystal was carefully glued onto a glass fiber; the needle axis was orientated parallel to the fiber axis. The glass fiber was glued to a standard size metal pin, and the pin was then mounted on a standard goniometer head.

Orientation of the Crystal and Collection of Intensity Data

The crystal was aligned on a Buerger precession camera by the methods described elsewhere[31] using Mo Kα radiation (λ = 0.7093 Å). The orientation photographs showed zones at spindle settings of 121° 0' and 30° 0'. Zero and first upper level photographs at both of these spindle settings were taken, and all photographs possessed mirror-mirror symmetry, which placed the crystal in the orthorhombic system. The systematic zero level extinctions along the *h00* line when h = 2n+1, along the *0k0* line when k = 2n+1, and along the *00l* line when l = 2n+1, indicated the space group $P2_12_12_1$. A photograph was taken half way

between the zero and first level to investigate the possibility of the space group being face centered. The photograph showed no reflection; this substantiated the assignment of the space group as $P2_12_12_1$.

Film measurement of the reciprocal cell dimensions were a^* = 5.22 mm, b^* = 3.49 mm, and c^* = 2.78 mm.[†] The direct cell dimensions of a was calculated from a^* by the relationship a = 0.7093 Å × 60 mm/a^*. The direct cell dimensions b and c were obtained from analogous equations to give values of a = 8.17(2)Å, b = 12.22(2)Å, and c = 15.34(2)Å. The calculated density based on four molecules of Peptide III ($C_9H_{15}N_5O_3 \cdot 2HBr \cdot H_2O$, mol wt = 421.11) and a unit cell volume of 1531.5 Å^3 was 1.832(2)g cm^{-3}.

The goniometer, with the crystal intact, was transferred to a Weissenberg camera for collection of intensity data. After checking the alignment of the camera in relation to the X-ray beam, a rotational photograph was taken using nickel filtered Cu Kα radiation (λ = 1.539 Å) to check crystal alignment. A zero level photograph was exposed for 24 hr. From this photograph, an intense reflection was chosen to make a standard series of exposures. The spindle was set to align this reflection, and exposures were made on a film for 1, 2, 5, 10, and 20 min by moving the camera carriage 4 mm between each exposure. The one minute exposure was just visible on the developed film; for this reason it was chosen as the time increment for a more complete series

---

[†]Reciprocal cell translations are given in mm on the basis of a sphere of reflection of 60 mm radius. Since the value 60 mm corresponds to the crystal to film distance of the precession camera, reciprocal cell translations were measured directly from the film.[32]

of exposures. Standard exposures of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, and 40 min were made on a single film. This constituted the series of intensities with which the observed intensity data were compared.

The layer photographs were made using the conventional Weissenburg geometry[39] by placing three films, separated by thin paper, into the camera and exposing for 24 hr. Photographs were obtained for each of the hkl ($h = 0,7$) levels. In addition, the hkl ($h = 0,4$) levels required a fourth film exposed for one hour. The three (or four) photographs for each level were developed simultaneously. The intensities were estimated visually by comparing each reflection with the standard series of intensities prepared from the same crystal.

Film factors were obtained by recording the intensity of 80 pairs of reflections, which could be read accurately on two films, and computing the average ratio of these intensities. The average value of the ratios of the intensities obtained for the first:second and second:third films for all eight levels was 2.34(6).

A total of 1031 independent reflections were read and corrected for Lorentz and polarization effects.[34] The linear absorption coefficient (μ) for viocidic acid was computed from the mass absorption coefficients (μ/ρ) by means of 1,[35] where p_i is the weight fraction of

$$\mu = G \sum_{i=1}^{n} p_i \left(\frac{\mu}{\rho}\right)_i \qquad (1)$$

element i in the crystal and G is the density. Values for (μ/ρ) were

obtained from *International Tables for X-ray Crystallography*.[36] The linear absorption coefficient so computed was $\mu = 77.54\ cm^{-1}$. Absorption corrections were computed assuming the crystal was a cylinder of mean radius 0.1 mm.[37] No extinction corrections were made.

Structure Solution and Refinement

The structure of viocidic acid was determined by a conventional application of the heavy atom method.[38] A three-dimensional Patterson[39] synthesis calculated[34] from the corrected intensity data revealed a set of high intensity vectors consistent with the $P2_12_12_1$ space group. The fractional coordinates of the two bromide ions were obtained from these vectors, and a structure factor calculation based on these coordinates ($x_1 = 0.56$, $y_1 = 0.57$, $z_1 = 0.33$, $x_2 = 0.60$, $y_2 = 0.33$, $z_2 = -0.43$) gave a R_1 value of 0.2705, where R_1 is defined by Equation 2.[40]

$$R_1 = \frac{\sum \| F_{obsd} | - | F_{calcd} \|}{\sum | F_{obsd} |} \qquad (2)$$

An electron density map was calculated[34] where the phases of the F_{obsd} values were based on the two bromide ions. From this map it was possible to find six peaks for atoms that were in reasonable bonding distance of one another. Location of the remaining atoms was achieved by a sequence of (1) a structure factor calculation, based on the coordinates of atoms previously located to obtain phased F_{obsd} values and (2) an electron density Fourier calculation using the phased F_{obsd} values to obtain coordinates for additional atoms. A newly

located atom was considered valid when the atom coordinates refined to a stable position and the magnitude of the isotropic temperature factor was less than six. Several cycles of refinement[41] of all the atomic coordinates, scale factors, and isotropic temperature factors gave a R_1 value of 0.1305. Ten reflections suspected of being effected by extinction were removed from the data set.

All light atoms in the structure had been assigned as carbon. The three atoms that had low isotropic temperature factors (0.1-0.3) were all in logical positions for water molecules and were assigned as oxygen atoms. The process of refining coordinates and isotropic temperature factors was repeated for ten cycles. This revealed five atoms that had low isotropic temperature factors (0.2-0.8), and these were assigned as nitrogen atoms. An additional five cycles of refining all atomic coordinates, scale factors, and isotropic temperature factors gave an R_1 value of 0.1101.

All refinements were full matrix least-squares, and the function minimized is given in Equation 3, where w is the weight assigned to a particular reflection. All previous refinements were based on unit

$$E = \sum w(|F_{obsd}| - |F_{calcd}|)^2 \qquad (3)$$

weights for all reflections. Since it was possible to measure the intensity of some reflections more accurately than others, a weighting scheme was devised to give the less accurate reflections less weight. It was possible to measure intensities (I) between 6 and 14 most

accurately. Any reflection that had an intensity less than 6 was assigned a weight $w = \sqrt{I/6}$. Intensities greater than or equal to 6 and less than or equal to 70 were assigned unit weight ($w = 1$). The value 70 was chosen rather than 14 because 14 × film factor^2 ≅ 70. Intensities greater than 70 were assigned weights $w = \sqrt{70/I}$. Several cycles of refinement using the weighting scheme yielded an R_1 value of 0.1095 and an R_2 value of 0.1141, where R_2 is defined by Equation 4.[37]

$$R_2 = \left[\frac{\sum w(|F_{obsd}| - |F_{calcd}|)^2}{\sum w F_{obsd}^2}\right]^{1/2} \qquad (4)$$

The isotropic temperature factors of the two bromide ions were converted to anisotropic temperature factors. Refinement of all atomic coordinates, scale factors, and anisotropic temperature factors using the weighting scheme on 1021 reflections yielded an R_1 value of 0.0901 and an R_2 value of 0.0950. The values of R_1 and R_2 for the 910 reflections that were greater than their estimated standard deviations were 0.0852 and 0.0946, respectively.

To determine the absolute configuration of viocidic acid, it was necessary to correct the scattering factor of the bromide ions for the real ($\Delta f'$) and imaginary ($\Delta f''$) portions of anomalous dispersion. The corrections[42] for the real portion of the anomalous dispersion were: $\Delta f' = -0.9$, $\sin\theta/\lambda = 0$; $\Delta f' = -1.0$, $\sin\theta/\lambda = 0.6$. Values of $\Delta f'$ for intermediate $\sin\theta/\lambda$ were obtained by interpolation. Corrections for the imaginary portion were: $\Delta f'' = 1.5$, $\sin\theta/\lambda = 0$; $\Delta f'' = 1.4$,

$\sin\theta/\lambda$ = 0.4; $\Delta f''$ = 1.3, $\sin\theta/\lambda$ = 0.6. The two sets of coordinates corresponding to the two enantiomers shown by structures 6 and 6' gave R_1 values of 0.0901 and 0.0922 for enantiomer 6 and enantiomer 6', respectively, after eight cycles refining atomic coordinates, scale factor, and anisotropic temperature factors. Hamilton[43] proposed a significance test on the R factor ratio that has been applied to several determinations of absolute configuration.[44,45] The ratio of the R_1 values for the final refinement was 1.023. An application of Hamilton's[43] significance test resulted in the assignment of enantiomer 6 as the correct absolute configuration with a confidence level of better than 99.5 per cent. The observed structure factors and the calculated structure factors for the 1021 reflections are given in Table 2. The atomic coordinates, their estimated standard deviations, and the isotropic temperature factors are given in Table 3 for the non-hydrogen atoms of viocidic acid. A difference Fourier did not reveal any significant peaks.

Tables 2 and 3 appear on the following pages:

Table 2. Observed and Calculated Structure Factors for Viocidic Acid Dihydrobromide

H	K	L	FO	FC
0	0	4	11	12
0	0	8	97	94
0	0	10	90	89
0	0	12	78	84
0	0	14	14	11
0	1	3	49	54
0	1	4	126	125
0	1	5	98	98
0	1	7	71	70
0	1	8	64	62
0	1	9	39	33
0	1	10	27	20
0	1	13	28	24
0	1	15	60	58
0	1	16	37	38
0	2	1	36	44
0	2	2	45	43
0	2	3	95	100
0	2	4	30	24
0	2	5	33	31
0	2	6	90	88
0	2	7	52	55
0	2	8	28	22
0	2	9	81	81
0	2	11	81	87
0	2	12	41	31
0	2	14	31	30
0	3	1	27	26
0	3	2	97	99
0	3	3	151	159
0	3	4	77	83
0	3	5	78	78
0	3	6	90	99
0	3	7	61	57
0	3	9	68	69
0	3	10	36	31
0	3	11	23	15
0	3	12	52	49
0	4	0	17	11
0	4	1	127	133
0	4	2	30	32
0	4	3	105	110
0	4	4	27	27
0	4	5	84	83
0	4	6	14	12
0	4	7	36	31
0	4	8	45	43
0	4	9	71	68
0	4	10	32	29
0	4	11	23	16
0	4	13	56	56
0	5	1	108	115
0	5	2	71	65
0	5	3	52	52
0	5	4	9	9
0	5	6	46	54
0	5	7	32	31
0	5	8	34	31
0	5	9	73	75
0	5	10	44	36
0	5	11	36	33
0	5	12	20	15
0	5	13	37	33
0	6	0	34	32
0	6	1	35	36
0	6	2	62	59
0	6	3	25	21
0	6	4	37	37
0	6	5	42	41
0	6	6	91	91
0	6	7	12	4
0	6	9	23	19
0	6	10	31	29
0	6	11	24	16
0	6	14	43	51
0	7	1	104	110
0	7	2	105	116
0	7	3	49	49
0	7	4	39	41
0	7	5	48	48
0	7	6	17	16
0	7	7	63	60
0	7	8	42	38
0	7	9	46	40
0	7	10	67	71
0	7	12	31	27
0	7	14	21	13
0	8	0	98	100
0	8	2	49	48
0	8	3	56	52
0	8	4	28	25
0	8	5	75	74
0	8	8	39	32
0	8	9	24	22
0	8	10	46	45
0	8	12	33	31
0	8	13	17	15
0	9	1	45	41
0	9	2	23	13
0	9	4	91	95
0	9	5	19	13
0	9	7	20	20
0	9	8	61	60
0	9	9	31	36
0	9	12	37	40
0	10	1	63	56
0	10	3	46	44
0	10	4	39	37
0	10	6	37	36
0	10	7	81	85
0	10	8	31	28
0	10	11	37	35
0	10	12	25	24
1	0	2	37	29
1	0	3	45	45
1	0	7	55	54
1	0	8	65	68
1	0	11	17	12
1	0	12	28	24
1	0	13	49	48
1	0	14	22	19
1	1	1	44	44
1	1	2	85	96
1	1	3	82	88
1	1	4	30	25
1	1	5	61	59
1	1	6	27	23
1	1	7	48	48
1	1	8	34	30
1	1	9	71	69
1	1	10	59	63
1	1	11	56	54
1	1	12	25	23
1	1	13	32	31
1	1	15	22	18
1	2	0	55	59
1	2	1	73	78
1	2	2	114	119
1	2	3	67	60
1	2	5	34	27
1	2	6	88	98
1	2	7	49	49
1	2	8	17	13
1	2	9	52	51
1	2	10	46	42
1	2	11	46	43
1	2	12	31	28
1	2	13	26	22
1	2	14	41	48
1	2	15	25	24
1	2	16	23	24
1	3	0	90	104
1	3	1	109	123
1	3	2	123	134
1	3	3	68	67
1	3	4	77	81
1	3	5	65	67
1	3	6	31	27
1	3	7	93	100
1	3	8	64	63
1	3	9	42	36
1	3	10	47	44
1	3	11	37	36
1	3	12	32	29
1	3	13	26	23
1	3	14	37	38
1	3	15	25	19
1	3	16	20	20
1	4	0	132	144
1	4	1	110	121
1	4	2	23	27
1	4	3	39	37

Table 2. (Continued)

H	K	L	FO	FC
1	4	4	89	95
1	4	5	56	54
1	4	6	58	57
1	4	7	35	35
1	4	8	89	97
1	4	9	49	52
1	4	10	39	33
1	4	11	33	26
1	4	12	45	44
1	4	13	32	27
1	4	14	22	21
1	5	0	52	56
1	5	1	29	30
1	5	2	24	24
1	5	3	82	82
1	5	4	115	123
1	5	5	65	63
1	5	6	38	37
1	5	7	49	45
1	5	8	55	54
1	5	9	36	33
1	5	11	29	25
1	5	12	45	46
1	5	13	13	12
1	5	14	31	31
1	5	15	23	23
1	6	0	66	69
1	6	1	83	79
1	6	2	38	30
1	6	3	48	44
1	6	4	27	23
1	6	5	23	19
1	6	6	47	44
1	6	7	49	54
1	6	8	42	40
1	6	9	35	29
1	6	10	48	49
1	6	11	49	50
1	6	12	32	30
1	6	13	25	19
1	6	14	17	18
1	7	0	25	18
1	7	1	29	25
1	7	2	50	48
1	7	3	88	93
1	7	4	54	54
1	7	5	69	71
1	7	6	68	67
1	7	7	65	68
1	7	9	39	36
1	7	10	32	28
1	7	11	29	24
1	7	12	26	22
1	8	0	52	52
1	8	1	46	44
1	8	2	28	24
1	8	4	29	26
1	8	5	71	73
1	8	7	34	31
1	8	8	37	29
1	8	9	35	30
1	8	10	18	16
1	8	12	25	19
1	9	0	64	62
1	9	1	52	56
1	9	2	24	18
1	9	3	28	20
1	9	4	42	39
1	9	5	18	10
1	9	7	26	23
1	9	8	29	27
1	9	9	55	57
1	9	10	28	28
1	9	11	17	14
1	9	12	16	19
1	9	13	23	20
1	10	1	18	11
1	10	2	66	67
1	10	3	41	38
1	10	4	35	35
1	10	5	37	39
1	10	6	63	66
1	10	7	29	27
1	10	8	18	14
1	10	9	17	14
1	10	11	19	17
1	11	2	56	65
1	11	3	22	16
1	11	4	22	19
1	11	6	22	15
1	11	7	21	15
1	11	8	24	25
1	12	4	28	23
1	12	5	36	43
1	12	6	35	37
2	0	2	55	51
2	0	3	123	138
2	0	4	47	45
2	0	5	42	39
2	0	6	14	9
2	0	7	66	59
2	0	8	51	48
2	0	9	100	98
2	0	10	54	57
2	0	11	37	29
2	0	12	24	15
2	0	13	47	52
2	0	15	17	14
2	1	1	53	53
2	1	3	81	79
2	1	4	82	83
2	1	5	85	89
2	1	6	61	65
2	1	7	67	66
2	1	8	73	77
2	1	9	26	24
2	1	10	32	29
2	1	11	16	11
2	1	12	37	34
2	1	13	38	41
2	1	14	42	46
2	1	16	30	31
2	2	0	74	81
2	2	1	91	92
2	2	2	92	99
2	2	3	45	38
2	2	4	66	63
2	2	5	68	62
2	2	6	44	46
2	2	7	72	73
2	2	8	20	10
2	2	9	28	24
2	2	10	58	61
2	2	11	51	46
2	2	12	17	13
2	2	13	25	21
2	2	14	30	29
2	2	15	29	28
2	3	0	40	36
2	3	1	98	102
2	3	2	93	91
2	3	3	70	74
2	3	4	25	20
2	3	5	67	70
2	3	6	94	103
2	3	7	16	13
2	3	8	34	30
2	3	9	48	43
2	3	10	31	25
2	3	11	56	62
2	3	12	31	24
2	3	13	25	22
2	3	14	21	16
2	3	15	26	23
2	4	0	83	80
2	4	1	81	79
2	4	2	39	35
2	4	3	38	31
2	4	4	142	146
2	4	5	58	63
2	4	6	62	66
2	4	7	43	38
2	4	8	37	34
2	4	9	32	26
2	4	11	37	36
2	4	12	40	39
2	4	13	28	24
2	4	14	32	34
2	5	0	87	88
2	5	1	44	39
2	5	2	45	47
2	5	3	41	36

Table 2. (Continued)

H	K	L	FO	FC
2	5	4	39	40
2	5	6	10	6
2	5	7	28	24
2	5	8	65	72
2	5	9	41	36
2	5	10	49	47
2	5	11	40	34
2	5	12	36	39
2	5	13	21	14
2	6	0	24	21
2	6	1	73	77
2	6	2	67	59
2	6	3	65	63
2	6	4	32	24
2	6	5	56	56
2	6	6	58	59
2	6	7	65	66
2	6	8	20	13
2	6	9	24	19
2	6	10	17	12
2	6	11	47	50
2	6	12	28	30
2	6	13	17	12
2	6	14	20	21
2	7	0	59	64
2	7	1	77	79
2	7	2	68	67
2	7	3	49	45
2	7	4	44	39
2	7	5	19	14
2	7	6	43	43
2	7	7	41	43
2	7	8	46	52
2	7	9	31	34
2	7	10	25	24
2	7	11	35	39
2	7	12	17	17
2	7	13	16	13
2	7	14	18	18
2	8	0	73	77
2	8	1	42	37
2	8	2	30	22
2	8	3	36	32
2	8	4	56	56
2	8	5	32	29
2	8	6	37	31
2	8	7	25	24
2	8	8	38	33
2	8	9	44	49
2	8	10	31	28
2	8	11	24	24
2	8	12	37	39
2	8	13	19	22
2	8	14	19	17
2	9	0	24	17
2	9	1	34	29
2	9	2	24	16
2	9	3	52	54
2	9	4	46	51
2	9	5	74	80
2	9	6	28	20
2	9	7	18	14
2	9	8	22	19
2	9	9	28	28
2	9	10	17	12
2	9	11	20	20
2	9	12	21	19
2	10	1	58	62
2	10	2	47	52
2	10	3	22	16
2	10	4	12	9
2	10	5	12	11
2	10	6	25	18
2	10	7	30	26
2	10	8	12	11
2	10	9	26	26
2	10	11	18	18
2	10	10	41	44
2	11	2	36	32
2	11	3	40	37
2	11	5	35	37
2	11	6	49	51
2	11	7	26	25
3	0	3	65	71
3	0	4	120	131
3	0	6	35	32
3	0	7	22	19
3	0	8	70	77
3	0	9	32	29
3	0	11	24	27
3	0	12	39	33
3	0	13	12	8
3	0	14	21	20
3	1	1	50	46
3	1	2	39	38
3	1	3	118	125
3	1	4	39	33
3	1	5	32	28
3	1	6	45	41
3	1	7	60	63
3	1	8	62	63
3	1	9	46	40
3	1	10	36	34
3	1	11	45	51
3	1	12	53	57
3	1	13	12	13
3	1	14	17	14
3	2	0	42	47
3	2	1	34	37
3	2	2	52	46
3	2	3	85	86
3	2	5	70	80
3	2	6	47	45
3	2	7	59	61
3	2	8	35	34
3	2	10	47	50
3	2	11	27	25
3	2	12	39	39
3	2	13	17	16
3	3	0	60	55
3	3	1	80	80
3	3	2	42	33
3	3	3	38	32
3	3	4	56	52
3	3	5	57	50
3	3	6	104	112
3	3	7	57	57
3	3	8	49	43
3	3	9	27	22
3	3	10	36	31
3	3	11	42	41
3	3	13	21	18
3	3	14	29	26
3	4	1	115	128
3	4	2	11	13
3	4	3	58	63
3	4	4	61	59
3	4	5	20	16
3	4	6	57	58
3	4	7	21	13
3	4	8	35	35
3	4	9	87	95
3	4	11	25	24
3	4	12	25	21
3	4	13	21	24
3	5	0	27	20
3	5	1	57	57
3	5	2	35	34
3	5	3	71	79
3	5	4	36	27
3	5	5	66	68
3	5	6	56	51
3	5	7	38	32
3	5	8	16	11
3	5	9	40	34
3	5	10	27	23
3	5	11	12	10
3	5	12	21	22
3	5	13	42	47
3	6	0	16	11
3	6	1	36	30
3	6	2	92	105
3	6	3	55	50
3	6	4	44	39
3	6	5	40	38
3	6	6	65	66
3	6	7	11	8
3	6	8	34	29
3	6	9	27	22
3	6	10	57	62
3	6	11	12	13

Table 2. (Continued)

H	K	L	FO	FC
3	6	12	24	22
3	7	0	40	34
3	7	1	30	27
3	7	2	57	58
3	7	3	53	48
3	7	4	45	40
3	7	5	26	20
3	7	6	57	60
3	7	7	17	14
3	7	8	27	29
3	7	9	28	27
3	7	10	25	24
3	7	11	24	23
3	7	12	26	27
3	8	1	61	58
3	8	2	40	34
3	8	4	63	68
3	8	5	34	29
3	8	6	12	11
3	8	7	53	56
3	8	8	47	49
3	8	9	37	39
3	8	10	27	23
3	8	12	19	14
3	9	0	92	98
3	9	1	27	21
3	9	2	21	16
3	9	4	21	16
3	9	5	33	31
3	9	6	25	20
3	9	7	43	44
3	9	8	43	47
3	9	10	31	29
3	9	11	19	18
3	10	1	17	13
3	10	2	21	14
3	10	3	43	45
3	10	4	41	42
3	10	5	35	33
3	10	6	12	11
3	10	7	34	33
3	10	8	23	19
3	11	2	17	17
3	11	3	32	33
3	11	4	27	27
3	11	7	36	38
4	0	2	41	37
4	0	3	25	17
4	0	4	37	36
4	0	5	60	66
4	0	6	28	31
4	0	7	29	28
4	0	8	51	51
4	0	9	70	71
4	0	13	22	20
4	1	1	68	72
4	1	2	43	41
4	1	3	45	37
4	1	4	44	44
4	1	5	115	107
4	1	6	77	86
4	1	7	48	38
4	1	8	50	40
4	1	9	29	26
4	1	13	51	52
4	2	0	76	75
4	2	1	18	19
4	2	2	87	80
4	2	3	71	78
4	2	4	38	33
4	2	5	45	45
4	2	6	30	21
4	2	7	49	46
4	2	8	26	24
4	2	9	23	23
4	2	10	76	76
4	2	11	37	40
4	3	0	67	64
4	3	1	52	59
4	3	2	55	54
4	3	3	64	62
4	3	4	63	70
4	3	5	29	23
4	3	6	53	58
4	3	7	21	17
4	3	8	30	28
4	3	9	10	3
4	3	10	45	48
4	3	11	30	31
4	3	12	39	44
4	4	0	60	68
4	4	1	40	36
4	4	2	51	47
4	4	3	43	38
4	4	4	94	96
4	4	5	60	67
4	4	6	25	23
4	4	7	38	32
4	4	8	51	55
4	4	9	24	25
4	4	10	22	18
4	4	11	25	27
4	4	12	30	31
4	4	13	29	23
4	5	0	65	73
4	5	1	75	80
4	5	2	8	3
4	5	3	31	24
4	5	4	40	35
4	5	5	39	38
4	5	6	35	33
4	5	7	46	47
4	5	8	60	63
4	5	9	37	33
4	5	10	23	19
4	5	11	25	24
4	5	12	29	32
4	5	13	21	19
4	6	0	32	31
4	6	1	43	37
4	6	2	28	37
4	6	3	65	67
4	6	4	30	27
4	6	5	55	57
4	6	6	37	39
4	6	7	56	56
4	6	8	37	37
4	6	9	16	17
4	6	10	19	21
4	6	11	22	19
4	6	12	15	12
4	6	13	14	14
4	7	1	59	62
4	7	2	31	31
4	7	3	23	20
4	7	4	34	28
4	7	5	41	42
4	7	6	25	21
4	7	7	34	32
4	7	8	20	11
4	7	9	23	18
4	7	10	25	23
4	7	11	30	32
4	7	12	14	10
4	8	0	26	24
4	8	1	36	32
4	8	2	33	27
4	8	3	63	67
4	8	4	59	63
4	8	5	25	20
4	8	6	36	32
4	8	7	19	22
4	8	8	11	8
4	8	9	47	51
4	8	10	10	8
4	8	11	23	25
4	9	0	36	32
4	9	1	19	16
4	9	2	34	27
4	9	3	16	8
4	9	4	38	36
4	9	5	36	39
4	9	6	36	34
4	9	7	22	21
4	9	8	19	18
4	9	9	15	15
4	10	2	53	55
4	10	3	32	28
4	10	5	19	19

Table 2. (Continued)

H	K	L	FO	FC
4	10	6	22	16
4	10	8	25	24
4	10	9	27	30
5	0	2	44	48
5	0	3	58	53
5	0	4	58	60
5	0	5	65	67
5	0	7	13	7
5	0	8	38	33
5	0	9	18	22
5	0	10	30	35
5	0	11	32	31
5	0	13	38	38
5	0	14	17	20
5	1	1	77	79
5	1	2	54	63
5	1	3	31	29
5	1	4	60	59
5	1	5	27	25
5	1	6	31	31
5	1	7	36	36
5	1	8	41	39
5	1	9	50	50
5	1	10	45	49
5	1	11	28	28
5	1	12	30	30
5	1	13	22	18
5	1	14	20	15
5	2	0	26	25
5	2	1	51	50
5	2	2	79	91
5	2	3	46	40
5	2	4	31	34
5	2	5	42	39
5	2	6	60	67
5	2	7	31	23
5	2	8	60	67
5	2	9	35	37
5	2	10	25	21
5	2	11	25	26
5	2	12	11	5
5	3	1	70	72
5	3	2	39	34
5	3	3	23	25
5	3	4	39	37
5	3	5	42	34
5	3	7	59	63
5	3	8	21	15
5	3	9	25	17
5	3	10	22	15
5	3	11	19	19
5	3	13	28	29
5	4	0	49	55
5	4	1	47	38
5	4	2	8	10
5	4	3	62	66
5	4	4	16	13
5	4	5	46	48
5	4	6	10	10
5	4	8	47	48
5	4	9	36	36
5	4	10	28	27
5	4	11	19	16
5	4	12	22	19
5	4	13	14	11
5	5	0	41	40
5	5	1	49	44
5	5	2	40	36
5	5	3	16	15
5	5	4	69	69
5	5	5	47	45
5	5	6	46	48
5	5	7	44	47
5	5	8	16	10
5	5	9	16	16
5	5	10	16	16
5	5	11	25	25
5	5	12	28	31
5	5	13	22	25
5	6	1	61	59
5	6	2	47	48
5	6	3	45	42
5	6	4	21	14
5	6	5	29	24
5	6	6	22	13
5	6	7	28	20
5	6	8	25	24
5	6	9	32	35
5	6	10	29	28
5	6	11	40	47
5	6	12	17	15
5	7	0	65	71
5	7	1	32	28
5	7	2	38	33
5	7	3	31	24
5	7	4	41	38
5	7	5	37	32
5	7	6	42	46
5	7	7	34	32
5	7	8	16	16
5	7	10	28	25
5	7	11	17	19
5	7	12	18	21
5	8	0	57	56
5	8	1	37	31
5	8	2	48	48
5	8	3	32	27
5	8	4	43	45
5	8	5	40	34
5	8	6	34	31
5	8	7	22	17
5	8	8	41	48
5	8	9	24	19
5	8	10	22	22
5	9	0	30	27
5	9	1	48	51
5	9	4	28	21
5	9	6	11	12
5	9	7	34	33
5	9	8	25	23
5	9	9	29	31
5	10	0	15	11
5	10	1	11	9
5	10	2	31	29
5	10	3	41	45
5	10	4	10	12
5	10	5	23	23
5	10	6	20	21
5	10	7	17	18
5	10	8	13	14
5	11	1	27	28
5	11	2	35	41
5	11	3	10	1
5	11	4	20	20
5	11	5	19	20
5	11	6	20	20
6	0	2	13	13
6	0	3	50	61
6	0	4	27	21
6	0	7	25	20
6	0	8	43	46
6	0	9	10	15
6	0	10	24	24
6	0	11	15	10
6	0	12	28	34
6	1	1	45	47
6	1	2	18	13
6	1	3	43	40
6	1	4	56	56
6	1	5	33	26
6	1	7	50	53
6	1	8	38	33
6	1	9	21	14
6	1	10	21	19
6	1	11	14	12
6	1	12	22	21
6	2	0	5	1
6	2	1	45	44
6	2	2	28	22
6	2	3	55	59
6	2	4	57	57
6	2	5	8	5
6	2	6	54	60
6	2	7	52	61
6	2	8	20	17
6	2	9	33	34
6	2	10	15	9
6	2	11	27	27

Table 2. (Continued)

H	K	L	FO	FC
6	2	12	20	24
6	3	0	19	16
6	3	1	47	41
6	3	2	50	42
6	3	3	43	35
6	3	4	41	39
6	3	5	30	25
6	3	6	44	44
6	3	7	10	8
6	3	8	25	20
6	3	9	37	39
6	3	10	32	37
6	3	11	18	20
6	3	12	27	34
6	4	0	42	40
6	4	1	26	18
6	4	2	44	41
6	4	3	47	52
6	4	4	16	14
6	4	5	51	53
6	4	6	43	41
6	4	10	21	26
6	4	8	28	24
6	4	7	41	43
6	4	9	23	20
6	5	0	20	17
6	5	1	65	74
6	5	2	54	54
6	5	3	30	25
6	5	4	17	11
6	5	5	30	30
6	5	6	44	42
6	5	7	26	19
6	5	8	21	17
6	5	9	45	52
6	5	10	20	24
6	5	11	17	16
6	6	0	22	15
6	6	1	31	31
6	6	2	43	33
6	6	3	20	17
6	6	4	25	16
6	6	5	21	16
6	6	6	56	58
6	6	7	26	26
6	6	8	10	12
6	6	9	20	21
6	6	10	14	10
6	7	0	18	13
6	7	1	23	19
6	7	2	42	39
6	7	3	30	27
6	7	5	40	45
6	7	6	26	23
6	7	7	23	22
6	7	8	22	23
6	7	9	13	9
6	7	10	27	31
6	8	0	49	54
6	8	1	21	15
6	8	2	33	32
6	8	4	18	17
6	8	5	31	32
6	8	6	17	14
6	8	7	14	13
6	8	8	25	27
6	8	9	12	13
6	8	10	8	13
6	9	0	14	9
6	9	1	14	12
6	9	2	18	14
6	9	3	31	26
6	9	4	40	41
6	9	6	23	26
6	10	0	17	21
6	10	1	26	24
6	10	2	13	13
6	10	3	25	24
6	10	4	26	25
7	0	2	42	45
7	0	3	31	34
7	0	4	33	25
7	0	5	39	46
7	0	6	13	15
7	0	7	23	24
7	0	9	15	15
7	0	10	18	24
7	1	1	23	32
7	1	2	36	45
7	1	3	39	44
7	1	4	12	7
7	1	5	42	43
7	1	6	34	33
7	1	7	10	10
7	1	8	26	20
7	1	9	32	37
7	1	10	10	13
7	1	11	22	23
7	2	0	14	12
7	2	1	47	56
7	2	2	48	48
7	2	3	11	13
7	2	4	28	23
7	2	5	31	26
7	2	6	43	47
7	2	7	33	31
7	2	8	18	16
7	2	9	24	28
7	2	11	17	19
7	3	0	52	49
7	3	1	23	18
7	3	2	43	38
7	3	3	9	3
7	3	4	40	37
7	3	5	30	25
7	3	6	25	18
7	3	7	26	25
7	3	8	26	29
7	3	9	10	9
7	3	10	27	32
7	4	0	59	52
7	4	2	41	39
7	4	3	23	15
7	4	4	20	14
7	4	5	25	22
7	4	6	21	21
7	4	7	26	27
7	4	8	24	26
7	4	10	22	26
7	5	0	31	33
7	5	1	17	13
7	5	2	38	37
7	5	3	49	46
7	5	4	42	40
7	5	5	37	40
7	5	6	10	6
7	5	7	21	22
7	5	8	21	22
7	5	9	10	11
7	6	0	10	4
7	6	1	39	37
7	6	2	36	30
7	6	3	30	25
7	6	4	37	41
7	6	5	10	10
7	6	6	18	16
7	6	7	21	22
7	6	8	10	13
7	7	0	32	32
7	7	1	15	14
7	7	2	28	27
7	7	3	40	43
7	7	4	18	15
7	7	5	18	17
7	7	6	17	11
7	7	7	17	11
7	7	8	16	15
7	8	0	21	17
7	8	1	39	40
7	8	2	18	16
7	8	3	20	18
7	8	4	20	15
7	8	5	30	33
7	8	6	9	6
7	9	1	26	22
7	9	2	29	28
7	9	3	21	18
7	9	4	16	18

Table 3. Final Least-Squares Positional and Thermal Parameters for Viocidic Acid Dihydrobromide

Atom	x	y	z	B
Br(1)	0.5654(3)	0.5690(2)	0.3311(1)	*
Br(2)	0.5961(3)	0.3361(1)	-0.4329(1)	*
N(3)	0.2645(27)	0.3136(16)	0.2388(13)	2.91(53)
C(4)	0.3365(27)	0.3800(17)	0.1853(13)	1.63(49)
N(5)	0.2593(21)	0.4736(12)	0.1674(11)	1.51(38)
C(6)	0.3178(32)	0.5428(19)	0.0951(14)	2.64(65)
C(7)	0.4964(25)	0.5369(15)	0.0693(13)	1.44(47)
C(8)	0.5804(30)	0.4369(17)	0.1043(12)	2.03(47)
N(9)	0.4678(19)	0.3520(13)	0.1394(9)	1.56(36)
C(10)	0.6813(26)	0.3885(16)	0.0266(13)	1.61(50)
C(11)	0.7220(28)	0.2671(18)	0.0203(15)	2.10(58)
O(12)	0.8133(18)	0.2402(11)	0.0906(8)	1.37(34)
O(13)	0.6653(18)	0.2068(11)	-0.0324(9)	1.63(34)
N(14)	0.5622(22)	0.4128(12)	-0.0520(10)	1.29(36)
C(15)	0.4840(24)	0.5230(15)	-0.0359(12)	1.20(48)
C(16)	0.3066(28)	0.5345(16)	-0.0649(14)	2.11(53)
N(17)	0.2108(19)	0.5008(13)	0.0119(10)	1.76(34)
O(18)	0.5110(19)	0.4514(11)	-0.2401(9)	1.97(37)
O(19)	0.5873(26)	0.6772(14)	-0.2559(10)	3.65(44)
O(20)	0.6430(23)	0.3097(14)	0.3554(11)	3.76(50)

	β_{11}	β_{22}	β_{23}	β_{12}	β_{13}	β_{23}
*Br(1)	0.00987	0.00378	0.00359	-0.00074	-0.00035	-0.00019
*Br(2)	0.00911	0.00407	0.00363	0.00173	0.00017	0.00039

Hydrolysis of Viocidic Acid

A single crystal (*ca.* 1 mg) of viocidic acid dihydrobromide[6] was dissolved in 0.75 ml of 6*N* hydrochloric acid; this solution was heated for 24 hr on a steam bath under reflux. The hydrolysate was analyzed by tlc using silica gel HF_{254} plates in several solvent systems; the plates were sprayed with ninhydrin reagent, and the results are given in Table 4.

Table 4. Tlc Analysis of the Acid Hydrolysate of Viocidic Acid

Solvent	Hydrolysate	Viocidic Acid	DAPA	Viomycidine
BAW[a]	0.16 brown 0.27 blue 0.68 yellow	0.16 brown	0.33 brown	0.25 purple 0.32 purple
BAAAW[b]	0.27 brown 0.39 blue	0.27 brown	0.41 brown	0.18 purple 0.42 purple
Water	0.20 brown 0.46 blue 0.67 yellow	0.20 brown	0.42 brown	0.18 purple 0.47 purple

[a]BAW - *t*-butyl alcohol:acetic acid:water (2:1:1).

[b]BAAAW - *n*-butyl alcohol:acetone:acetic acid:5% aqueous ammonia:water (9:3:2:2:4).

2-(2,3-Dichloro-2-pyrrolin-1-yl)-1-pyrroline

Reaction of 2-Pyrrolidinone with Hydrogen Chloride and Phosphorous Pentachloride

Liquid 2-pyrrolidinone (30 g, 0.35 moles) maintained at 140° was saturated with hydrogen chloride. Addition of hydrogen chloride was discontinued, and the dark liquid became solid when cooled to *ca.* 70°. Phosphorous pentachloride (90 g, 0.43 moles) was added to the mixture with stirring and heating to *ca.* 90°. A vigorous reaction began as the two solids melted and continued with the evolution of a gas. The semisolid material was heated to 110° and that temperature was maintained with stirring for 15 min. The dark liquid was cooled to 0° in dry ice-acetone. Small chips of ice were carefully added, and the ensuing reaction was controlled by emersing the flask in dry ice-acetone. After the addition of *ca.* 20 ml of water and 1 g of Darco G-60 the mixture was slowly warmed to 20° and stirred for 15 min. The Darco G-60 was removed by vacuum filtration through a celite mat. The filtrate was cooled to 0° and cold 6*N* sodium hydroxide was added, with cooling, until a pH of *ca.* 11 was reached. A tan precipitate formed immediately and was collected. This material was washed with water and recrystallized from acetone-water (1:1) to yield brown needle crystals (*ca.* 7 g). These crystals were sublimed at 57° and 1 mm to yield 4.7625 g (13%) of 8: mp 50-51° [lit.[11] mp 50-51°]; uv max (95% C_2H_5OH) 262.5 nm (ϵ 1.49 x 10^4); ir (film) 3160, 2900, 2980, 2860, 1735, 1625, 1605, 1423 and 1230 k among others; 60 MHz nmr (CCl_4) τ 8.10 (m, 2), 7.31 (t, 2, J = 9 Hz), 7.10 (t, 2, J = 8 Hz), 6.45 (t, 2, J = 7 Hz), 6.00 (t, 2, J = 9 Hz), 100 MHz nmr spin

decoupling (CCl_4) irradiate τ 6.45 (8.10 became t, J = 8 Hz), irradiate τ 6.00 (7.30 became s), irradiate τ 7.10 (8.10 became t, J = 7 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 208(15), 207(21), 206(79), 205(61), 204 M^+(100), 203(60), 171(40), 170(15), 169(77), 138(30), 136(43), 133(22), 69(19), 68(22); emd M^+ 204.029(8) calcd 204.022.

Anal $C_8H_{10}N_2Cl_2$ (205.09) Calcd: C, 46.84; H, 4.91; N, 13.68
Found: C, 46.73; H, 5.02; N, 13.61

A solution of 24 in 95 per cent ethanol (*ca.* 20 mg in 2 ml) was added to 20 ml of 95 per cent ethanol that was *ca.* 1*N* in silver nitrate and 0.5*N* in nitric acid. After two hours no visible precipitate was present. A solution of 24 in acetone rapidly decolorized a solution of neutral potassium permanganate.

Preparation of (*E*)-2,3-Dichloro-1-(2-pyrrolidinylidene)-2-pyrrolinium bromide 25

A solution of 24 (*ca.* 1 g) in 100 ml of anhydrous ether was cooled to *ca.* 10° and treated with dry hydrogen bromide. The colorless precipitate was collected and washed with three 20 ml portions of anhydrous ether. The dried colorless material (*ca.* 1.2 g) was dissolved in a minimum amount of water at 60°. The solution was allowed to slowly cool, and the crystals that formed were collected mp > 200° dec; uv max (95% C_2H_5OH) 260.0 nm(ε 1.83×10^4); ir (KBr pellet) 3060, 3000, 2840, 1660, 1630 and 1500 k among others; 100 MHz nmr (TFA) at 20° τ 7.65 (m, 4), 6.96 (m, 4) 6.54 (5,4, J = 7.5 Hz), 6.21 (m, 4), 5.80 (m, 4), 2.05 (s,>1) and 1.65 (s,<1). The ratio of 1.65 τ to 2.05 τ was 1:2.43, at 40°C, 1:2.36, at -7°, 1:2.90.

Anal $C_8H_{10}N_2Cl_2 \cdot HBr$ (285.93) Calcd: C, 33.42; H, 4.01; N, 9.61
Found: C, 33.60; H, 3.85; N, 9.70

Collection of X-ray Film Data

Description and Mounting of the Crystal. A solution of 25 was crystallized from acetone-water (*ca.* 20:1) by allowing a warm saturated solution to cool slowly to 0°. An apparently single crystal of approximate dimensions 0.20 x 0.08 x 0.08 mm was selected. The density of a single crystal was determined by flotation in a solution of carbon tetrachloride and bromoethane and was found to be 1.67 g cm^{-3}. The crystal was mounted on a glass fiber, and the fiber was glued to a metal pin mounted on a standard goniometer head.

Orientation of the Crystal and Collection of Intensity Data. The crystal was aligned on a Buerger precession camera by methods described elsewhere[31] using Mo Kα radiation (λ = 0.7093 Å). Two zones were found at spindle settings of 96° 05' and 186° 05'; only the zone at 186° 05' showed mirror-mirror symmetry, which placed the crystal in the monoclinic system. The systematic extinctions in the *h0l* zone for $l = 2n+1$ and along the line *0k0* for $k = 2n+1$ indicated the space group $P2_1/c$.

Film measurements of the reciprocal cell dimensions were $a^* = 6.95$ mm, $b^* = 1.96$ mm, $c^* = 4.91$ mm, and $\beta^* = 67° 15'$. The direct cell dimensions calculated from these film measurements were $a = 6.64(2)$ Å, $b = 21.79(4)$ Å, $c = 9.42(2)$ Å and $\beta = 112° 45'$. The calculated density, based on four molecules of $(C_8H_{10}N_2Cl_2 \cdot HBr \cdot 2H_2O$, mol wt = 321.02) and a unit cell volume of 1256.9 $Å^3$, was 1.688(2) g cm^{-3}.

The crystal, which had been aligned with the a^* axis parallel to the spindle axis, was reoriented with the b axis parallel to the spindle axis. The crystal was transferred to a Weissenberg camera to collect intensity data. Alignment of the crystal on the Weissenberg camera was checked by taking a rotational photograph.

The layer photographs were obtained using the conventional Weissenberg geometry by placing three films, separated by thin paper, into the camera and exposing the films for 24 hr. Photographs were obtained for each of the hkl ($h = 0,4$) levels using Cu Kα radiation ($\lambda = 1.539$ Å). The three photographs for each level were developed simultaneously. The intensities were estimated visually by comparing each reflection with a standard series of intensities. A total of 1380 independent reflections were read and corrected for Lorentz and polarization effects.[34]

Attempted Structure Solution. A three-dimensional Patterson[39] synthesis calculated from the corrected intensity data revealed a set of vectors consistent with the $P2_1/c$ space group. Fractional coordinates for the bromide ion were obtained from these vectors, and a structure factor calculation[40] based on these coordinates gave an R_1 value of 0.3200. Attempts to locate atom positions from electron density maps and subsequent structure factor calculations were unsuccessful. Decomposition of the crystal was noticed only after the data had been collected and estimated. Because of this decomposition and the inability to refine the structure, the attempt to solve the structure from these film data was abandoned.

Collection of Diffractometer Data

Description and Mounting of the Crystal. A solution of 25 in distilled water was allowed to evaporate slowly. The small crystals (*ca.* 0.07 x 0.05 x 0.05 mm) that were obtained appeared from preliminary precession photographs to be twinned. However, these crystals had well formed faces and were physically stable (*i.e.* they did not lose solvent of crystallization). By slow evaporation of an aqueous solution of 25, large crystals (*ca.* 4 x 3 x 1 mm) were obtained. A crystal of suitable size was cut from one of these large crystals and mounted for preliminary precession photographs. The crystal produced a diffraction pattern unlike the crystals suspected of being twinned.

An approximately cube shaped (0.461 x 0.403 x 0.355 mm) crystal was cut from one of the large crystals using a razor blade. The density of several similar crystals was obtained by flotation in a solution of carbon tetrachloride and bromoethane and was found to be 1.687(2) g cm^{-3}.

The crystal was carefully glued onto a glass fiber; the longest dimension of the crystal was oriented perpendicular to the fiber axis. The glass fiber was glued to a standard size metal pin, and the pin was then mounted on a standard goniometer head.

Orientation of the Crystal. The crystal was aligned on a Buerger precession camera by the methods described elsewhere[31] using Mo Kα radiation (λ = 0.7093 Å). The orientation photographs showed zones at spindle settings of 95° 45' and 54° 00'. Zero level photographs at both spindle settings were taken, and both photographs

possessed mirror-mirror symmetry, which placed the crystal in the monoclinic system. Systematic extinctions along the line *0k0* $k = 2n+1$ and in the *hOl* zone for $l = 2n+1$ indicated the space group $P2_1/c$.

Film measurements of the reciprocal cell dimensions were $a^* = 6.96$, $b^* = 1.95$, $c^* = 6.81$ mm, and $\beta^* = 41° 51'$. The direct cell dimensions calculated from these measurements were $a = 9.21(2)$ Å $b = 21.88(4)$ Å, $c = 9.41(2)$ Å, and $\beta = 138° 15'(10)$.

Collection of Intensity Data. The goniometer, with the crystal intact, was transferred to an automated Picker four-circle diffractometer. The crystal was aligned according to Picker instructions.[46] The setting angles of ten reflections were manually optimized for maximum intensity. The setting angles of these ten reflections were used to refine unit cell dimensions by a least-squares procedure.[47] The unit cell dimensions obtained were $a = 9.193(2)$ Å, $b = 21.901(10)$ Å, $c = 9.428(3)$ Å, and $\beta = 138.166(20)°$ using Mo Kα radiation (λ = 0.7093 Å). The calculated density based on four molecules of 25 ($C_8H_{10}N_2Cl_2 \cdot HBr \cdot 2H_2O$, mol wt = 322.05) and a unit cell volume of 1266.0 Å^3 was 1.693(1) g cm^{-3}.

The intensity measurements were obtained from the same crystal used for unit cell measurements. The intensities were measured, using zirconium filtered Mo Kα radiation, with a scintillation counter mounted 21 cm from the crystal. The intensities were collected by the θ-2θ scan technique with a takeoff angle of 1.6° and a scan rate of 1° min^{-1}. A symmetrical scan of 2° was taken about the calculated

position for each reflection. Stationary background counts of 20 sec were taken at the end (B1) and the beginning (B2) of the 2θ scan. Calibrated copper attenuators were used in collecting the data.[42] The attenuation point was set so that the counting rate would not exceed 10,000 counts sec^{-1}. The pulse height analyzer was set for approximately a 90 per cent window centered on the Mo Kα peak.[49] A total of 2197 reflections were collected for h = -6,6, k = 0,12, and l = -6,6. The equivalent hkl and $\bar{h}k\bar{l}$ reflections were later averaged to give 1042 unique reflections.

Corrected intensities (CI) were obtained by subtracting three times the total background count from the total integrated peak count (CT) as shown in Equation 5. The background counts are multiplied

$$CI = CT - TST/2 \times SBT(B1+B2) \tag{5}$$

by three because this is the ratio of total scan time (TST) to twice the single background time (SBT). The corrected intensities were assigned standard deviations according to Equation 6,[50] where P is an

$$\sigma(CI) = [CT + 0.25(TST/SBT)^2(B1+B2) + (P \times CI)^2]^{1/2} \tag{6}$$

ignorance factor assigned by Ibers as between 0.05 and 0.01. A total of 640 reflections were accepted as statistically above background on the basis that σ(CI)/CI was less than 0.11 when P = 0.01.

A strip chart recorder monitored the scan of each reflection. This record was examined for erratic background and the inclusion of a peak from the Kβ of Mo radiation. Thirty-six reflections were removed from the data for these reasons.

Approximately every 100 reflections, three standard reflections were measured. The average of the last set of standards was *ca.* 88 per cent of their initial average value. A FORTRAN computer program was written* to scale the intensities according to the sets of standard reflections assuming a linear decrease in intensity between standards. The scaled intensities (SCI) were corrected for Lorentz and polarization effects. The linear absorption coefficient was calculated according to Equation 1, and was found to be $\mu = 33.5\ cm^{-1}$. Absorption corrections were made by assuming the crystal to be a sphere of mean radius 0.2 mm.[37] No extinction corrections were made.

Structure Solution and Refinement. A three-dimensional Patterson function was calculated using the 604 unique nonzero reflections. A set of high intensity vectors consistent with the $P2_1/c$ space group were found, and the fractional coordinates of the bromide ion were obtained from these vectors. A structure factor calculation based on these coordinates (x = 0.380, y = 0.325, z = 0.030) gave an R_2 value of 0.39. An electron density map computed from the F_{obsd} values, phased by the bromide ion, revealed positions for the two chlorine atoms. A structure factor calculation based on these three atoms gave

---

*See Appendix.

an R_2 value of 0.27. Subsequent electron density maps revealed positions for the 12 light atoms. All light atoms were initially assumed to be nitrogen atoms until their isotropic temperature factors dictated their assignment as carbon or oxygen. Several cycles, refining the atomic coordinates, scale factor, and isotropic temperature factors, yielded on R_2 value of 0.068. After further refinement with anisotropic temperature factors and a weighting scheme, based on counting statistics ($w = 4(CI)/\sigma(I)^2$), values of 0.082 and 0.049 were obtained for R_1 and R_2, respectively. Table 5 lists the observed and calculated structure factors for each *hkl*. Table 6 lists the final positional parameters for 25.

Tables 5 and 6 appear on the following pages:

Table 5. Observed and Calculated Structure Factors for 25

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
2	0	0	55	53	3	12	0	38	38	-1	6	1	54	54
3	0	0	28	32	4	12	0	39	40	1	6	1	47	42
4	0	0	13	12	-6	1	1	34	33	2	6	1	43	45
5	0	0	46	43	-5	1	1	36	35	-6	7	1	24	23
2	1	0	95	96	-4	1	1	48	48	-3	7	1	34	28
3	1	0	17	14	-2	1	1	17	21	-2	7	1	69	65
5	1	0	38	31	-1	1	1	39	42	-1	7	1	67	67
6	1	0	31	25	1	1	1	75	81	0	7	1	33	35
2	2	0	49	44	2	1	1	33	31	1	7	1	48	44
3	2	0	24	23	3	1	1	21	21	2	7	1	43	41
4	2	0	51	47	4	1	1	28	31	3	7	1	21	18
1	3	0	12	18	-6	2	1	26	25	6	7	1	21	19
2	3	0	18	16	-5	2	1	44	44	-6	8	1	26	23
3	3	0	51	47	-4	2	1	45	42	-5	8	1	28	26
4	3	0	33	33	-3	2	1	103	103	-3	8	1	65	63
0	4	0	41	43	-2	2	1	34	33	-2	8	1	24	25
1	4	0	41	44	0	2	1	46	39	-1	8	1	55	59
2	4	0	26	17	1	2	1	61	64	1	8	1	20	21
4	4	0	36	32	2	2	1	109	114	2	8	1	58	59
1	5	0	29	27	3	2	1	35	32	3	8	1	27	24
2	5	0	70	66	4	2	1	21	16	4	8	1	21	20
3	5	0	67	66	5	2	1	17	15	6	8	1	20	9
4	5	0	49	46	6	2	1	26	26	-6	9	1	26	21
5	5	0	21	16	-5	3	1	16	2	-5	9	1	28	28
6	5	0	32	29	-4	3	1	59	59	-4	9	1	42	39
0	6	0	132	119	-3	3	1	99	99	-3	9	1	52	49
1	6	0	97	95	-2	3	1	101	114	-2	9	1	19	15
2	6	0	54	53	1	3	1	51	52	0	9	1	85	83
3	6	0	72	69	2	3	1	30	30	1	9	1	110	109
4	6	0	61	59	3	3	1	56	56	2	9	1	46	46
5	6	0	20	14	4	3	1	40	43	3	9	1	27	28
1	7	0	100	99	5	3	1	20	19	4	9	1	37	38
2	7	0	81	80	-5	4	1	28	23	6	9	1	21	18
3	7	0	17	10	-4	4	1	19	16	-6	10	1	33	35
4	7	0	17	2	-3	4	1	20	17	-5	10	1	52	53
5	7	0	41	39	-2	4	1	267	290	-4	10	1	22	17
6	7	0	23	21	0	4	1	14	9	-3	10	1	32	36
0	8	0	183	172	1	4	1	38	43	-2	10	1	46	49
2	8	0	12	4	3	4	1	78	78	-1	10	1	76	79
3	8	0	25	21	5	4	1	36	37	1	10	1	46	46
5	8	0	27	21	6	4	1	19	14	2	10	1	76	78
6	8	0	21	18	-4	5	1	60	62	3	10	1	30	31
1	9	0	74	68	-3	5	1	46	42	-4	11	1	53	56
2	9	0	35	33	-2	5	1	65	60	-3	11	1	61	62
3	9	0	16	14	-1	5	1	41	56	-1	11	1	54	55
4	9	0	17	11	0	5	1	44	45	0	11	1	47	47
0	10	0	57	66	1	5	1	42	43	2	11	1	15	7
1	10	0	17	13	2	5	1	23	21	3	11	1	41	42
2	10	0	39	39	3	5	1	27	27	4	11	1	34	33
4	10	0	16	10	4	5	1	37	39	5	11	1	21	24
2	11	0	32	30	5	5	1	18	9	6	11	1	20	12
3	11	0	17	15	6	5	1	20	17	-3	12	1	33	37
4	11	0	30	29	-6	6	1	26	20	-2	12	1	87	92
5	11	0	28	23	-5	6	1	21	18	-1	12	1	26	26
6	11	0	19	13	-4	6	1	36	34	1	12	1	15	9
1	12	0	70	75	-2	6	1	41	39	3	12	1	34	37

Table 5. (Continued)

H	K	L	FO	FC
5	12	1	21	26
-5	0	2	19	20
-4	0	2	103	101
-3	0	2	70	76
0	0	2	10	0
1	0	2	141	143
3	0	2	62	61
4	0	2	24	23
-6	1	2	41	41
-5	1	2	63	62
-4	1	2	30	28
-3	1	2	39	39
0	1	2	67	62
1	1	2	54	54
2	1	2	48	51
3	1	2	37	35
-6	2	2	33	27
-5	2	2	43	39
-4	2	2	14	10
-3	2	2	31	37
1	2	2	41	41
2	2	2	15	13
4	2	2	24	26
5	2	2	21	16
-6	3	2	22	18
-4	3	2	41	40
-3	3	2	65	65
-2	3	2	38	51
-1	3	2	53	53
0	3	2	33	32
2	3	2	27	29
3	3	2	18	17
4	3	2	23	20
-5	4	2	22	20
-3	4	2	26	28
-2	4	2	25	25
-1	4	2	36	29
0	4	2	20	18
1	4	2	42	41
2	4	2	21	21
3	4	2	29	28
4	4	2	20	19
-6	5	2	34	31
-5	5	2	57	59
-2	5	2	29	32
-1	5	2	173	148
0	5	2	19	17
1	5	2	30	30
2	5	2	29	29
4	5	2	38	38
5	5	2	23	16
-6	6	2	24	19
-5	6	2	35	30
-4	6	2	13	3
-3	6	2	42	47
-2	6	2	33	35
-1	6	2	24	19
0	6	2	150	144
1	6	2	70	70
3	6	2	19	21
4	6	2	28	30
5	6	2	22	23
-6	7	2	38	35
-5	7	2	51	49
-4	7	2	47	48
-3	7	2	26	19
-2	7	2	83	85
-1	7	2	51	46
0	7	2	34	31
1	7	2	63	62
2	7	2	64	66
3	7	2	37	38
4	7	2	22	23
-5	8	2	16	14
-4	8	2	124	127
-3	8	2	57	57
-2	8	2	20	24
-1	8	2	52	45
0	8	2	24	24
1	8	2	83	86
3	8	2	31	34
4	8	2	24	26
-6	9	2	19	18
-4	9	2	21	19
-2	9	2	13	9
0	9	2	50	50
2	9	2	31	36
4	9	2	19	17
-6	10	2	18	11
-5	10	2	17	15
-4	10	2	41	41
-1	10	2	58	55
0	10	2	39	38
1	10	2	46	43
3	10	2	22	24
-5	11	2	26	24
-4	11	2	48	55
-3	11	2	33	32
-2	11	2	60	64
0	11	2	22	16
3	11	2	23	15
-5	12	2	31	32
-4	12	2	22	19
-3	12	2	38	42
0	12	2	97	95
1	12	2	36	37
2	12	2	29	28
4	12	2	23	14
-5	1	3	16	17
-4	1	3	20	18
-3	1	3	92	97
-2	1	3	14	20
0	1	3	35	33
2	1	3	57	58
3	1	3	22	19
4	1	3	23	20
-5	2	3	45	45
-4	2	3	30	31
-3	2	3	50	48
-2	2	3	172	155
-1	2	3	78	73
0	2	3	28	24
2	2	3	20	24
3	2	3	41	42
-6	3	3	22	18
-5	3	3	13	10
-4	3	3	68	71
-3	3	3	85	86
-2	3	3	42	43
-1	3	3	32	27
0	3	3	80	77
1	3	3	78	82
2	3	3	17	17
4	3	3	20	21
-6	4	3	51	45
-5	4	3	62	62
-4	4	3	66	71
-3	4	3	56	61
-2	4	3	48	43
-1	4	3	144	139
0	4	3	17	11
1	4	3	40	42
2	4	3	42	46
3	4	3	17	19
-6	5	3	28	26
-4	5	3	48	52
-3	5	3	86	86
-2	5	3	82	77
0	5	3	32	31
1	5	3	37	37
3	5	3	18	8
-4	6	3	15	9
-3	6	3	12	7
-2	6	3	83	81
3	6	3	27	26
-6	7	3	30	29
-5	7	3	31	29
-4	7	3	68	71
-3	7	3	15	13
-1	7	3	51	48
0	7	3	13	18
1	7	3	62	62
2	7	3	20	14
-5	8	3	24	24
-2	8	3	72	71
-1	8	3	50	48
0	8	3	29	20
1	8	3	24	31

Table 5. (Continued)

H	K	L	FO	FC
2	8	3	25	28
3	8	3	20	13
-4	9	3	26	29
-3	9	3	85	92
-2	9	3	47	46
-1	9	3	13	7
0	9	3	49	48
2	9	3	43	46
3	9	3	24	19
4	9	3	22	11
-6	10	3	16	11
-5	10	3	38	39
-4	10	3	43	48
-3	10	3	18	19
-2	10	3	99	100
-1	10	3	55	57
1	10	3	25	29
2	10	3	42	51
3	10	3	33	39
-6	11	3	43	45
-4	11	3	36	34
-3	11	3	43	46
-2	11	3	46	47
-1	11	3	53	53
0	11	3	50	53
1	11	3	51	53
-6	12	3	31	22
-5	12	3	22	20
-4	12	3	18	23
-3	12	3	30	32
-2	12	3	25	22
-1	12	3	36	34
0	12	3	21	20
-6	0	4	63	65
-5	0	4	54	56
-4	0	4	58	58
-3	0	4	102	105
-2	0	4	53	47
0	0	4	87	87
1	0	4	28	37
4	0	4	24	28
-6	1	4	39	39
-5	1	4	50	52
-4	1	4	59	57
-3	1	4	23	23
-2	1	4	63	60
-1	1	4	101	97
0	1	4	18	16
1	1	4	17	13
2	1	4	27	34
-6	2	4	24	22
-5	2	4	32	33
-4	2	4	81	84
-2	2	4	26	21
-1	2	4	18	8
0	2	4	16	11
1	2	4	58	62
2	2	4	30	33
3	2	4	20	20
-6	3	4	18	11
-5	3	4	35	38
-4	3	4	21	5
-3	3	4	30	32
-1	3	4	33	32
0	3	4	54	49
-6	4	4	23	20
-4	4	4	56	53
-3	4	4	12	6
-1	4	4	21	11
0	4	4	22	10
1	4	4	21	15
2	4	4	19	17
-6	5	4	15	13
-5	5	4	45	48
-4	5	4	46	48
-2	5	4	78	74
0	5	4	67	67
1	5	4	18	18
2	5	4	33	33
3	5	4	25	25
-6	6	4	34	34
-5	6	4	19	16
-4	6	4	75	84
-3	6	4	50	46
-1	6	4	32	28
0	6	4	50	51
1	6	4	59	64
2	6	4	25	23
3	6	4	20	18
-6	7	4	34	32
-5	7	4	64	66
-4	7	4	52	49
-3	7	4	23	14
-2	7	4	57	54
-1	7	4	120	117
0	7	4	21	23
2	7	4	21	28
-6	8	4	40	38
-5	8	4	27	27
-4	8	4	16	11
-3	8	4	71	72
-2	8	4	29	27
0	8	4	32	28
1	8	4	18	25
4	8	4	21	26
-6	9	4	20	23
-5	9	4	38	42
-2	9	4	15	12
-1	9	4	26	24
1	9	4	17	13
-6	10	4	27	18
-5	10	4	17	22
-4	10	4	23	29
-3	10	4	20	13
0	10	4	26	26
1	10	4	19	22
3	10	4	20	18
-6	11	4	37	37
-5	11	4	20	22
-4	11	4	32	38
-3	11	4	23	17
-2	11	4	19	22
-1	11	4	75	76
-4	12	4	35	22
-3	12	4	38	36
-2	12	4	42	41
-1	12	4	28	35
0	12	4	28	35
1	12	4	29	26
-6	1	5	35	36
-4	1	5	38	42
-3	1	5	35	29
-2	1	5	52	50
1	1	5	31	29
-6	2	5	37	34
-5	2	5	22	19
-4	2	5	22	18
-3	2	5	25	22
-2	2	5	20	17
-1	2	5	85	84
0	2	5	59	63
1	2	5	25	29
2	2	5	22	24
-6	3	5	46	47
-4	3	5	36	36
-3	3	5	137	136
-2	3	5	70	69
-1	3	5	21	16
0	3	5	36	43
2	3	5	23	24
-5	4	5	57	59
-4	4	5	63	63
-3	4	5	47	42
-2	4	5	64	60
-1	4	5	37	43
2	4	5	26	34
3	4	5	21	19
-6	5	5	15	7
-5	5	5	15	15
-4	5	5	17	13
-3	5	5	76	73
-2	5	5	16	15
-1	5	5	15	15
0	5	5	17	19
1	5	5	19	20
2	5	5	20	18
-6	6	5	30	31
-4	6	5	16	10

Table 5. (Continued)

H	K	L	FO	FC
-3	6	5	14	9
-2	6	5	32	30
-1	6	5	46	46
0	6	5	19	17
1	6	5	18	16
-6	7	5	25	26
-3	7	5	43	41
-2	7	5	18	18
1	7	5	19	16
2	7	5	21	20
-6	8	5	23	17
-5	8	5	21	17
-4	8	5	42	43
-2	8	5	16	15
-1	8	5	37	36
0	8	5	22	21
2	8	5	22	18
3	8	5	22	13
-6	9	5	31	35
-4	9	5	63	65
-3	9	5	26	24
-2	9	5	71	72
0	9	5	37	39
1	9	5	51	55
-6	10	5	25	20
-5	10	5	44	47
-4	10	5	23	19
-2	10	5	30	28
-1	10	5	52	55
0	10	5	27	27
-6	11	5	16	7
-4	11	5	27	24
-3	11	5	80	80
0	11	5	25	28
-5	12	5	28	38
-4	12	5	28	33
-3	12	5	19	18
-2	12	5	36	39
-1	12	5	18	18
-6	0	6	59	58
-5	0	6	65	67
-4	0	6	32	32
-3	0	6	56	58
-1	0	6	17	13
0	0	6	25	33
1	0	6	32	36
2	0	6	22	19
-5	1	6	94	96
-4	1	6	49	53
-2	1	6	19	20
-1	1	6	22	26
0	1	6	39	46
-6	2	6	17	18
-5	2	6	18	18
-3	2	6	51	53
-2	2	6	42	41
-5	3	6	33	33
-4	3	6	15	15
-1	3	6	32	28
-6	4	6	15	16
-3	4	6	27	29
-1	4	6	17	19
-6	5	6	39	40
-5	5	6	15	11
-4	5	6	43	43
-3	5	6	21	17
-1	5	6	72	75
0	5	6	19	9
-6	6	6	38	35
-5	6	6	15	8
-3	6	6	71	72
-2	6	6	65	66
0	6	6	21	27
-6	7	6	17	11
-5	7	6	74	75
-4	7	6	44	44
-2	7	6	42	46
0	7	6	31	40
-6	8	6	48	52
-5	8	6	39	39
-4	8	6	54	57
-3	8	6	21	20
-1	8	6	18	19
1	8	6	24	27
-5	9	6	18	17
-4	9	6	22	28
-2	9	6	17	22
-6	10	6	19	19
-5	10	6	24	26
-4	10	6	34	37
-2	10	6	25	27
-5	11	6	26	23
-4	11	6	16	4
-3	11	6	18	13
-2	11	6	18	15
0	11	6	27	30
-6	12	6	39	40
-5	12	6	19	17
-3	12	6	33	36
-2	12	6	33	31

Table 6. Final Least-Squares Positional Parameters for 25

Atom	x	y	z
Br(1)	0.3676(4)	0.3271(1)	0.0219(4)
Cl(2)	0.7979(9)	0.5600(4)	0.7770(9)
Cl(3)	0.9642(10)	0.4452(4)	0.6967(10)
C(4)	0.4899(42)	0.5464(13)	0.1812(39)
N(5)	0.5251(29)	0.5754(11)	0.3527(26)
N(6)	0.2661(27)	0.6498(10)	0.1238(26)
C(7)	0.4457(34)	0.6571(12)	0.4775(32)
O(8)	0.1456(23)	0.8685(8)	0.2546(22)
C(9)	0.4161(35)	0.6209(14)	0.3155(31)
C(10)	0.2488(39)	0.7003(11)	0.3350(37)
C(11)	0.6315(36)	0.4893(13)	0.2767(34)
C(12)	0.1712(40)	0.7027(13)	0.1193(40)
O(13)	0.7670(24)	0.6947(7)	0.4135(22)
C(14)	0.7616(38)	0.4946(15)	0.5105(36)
C(15)	0.7070(35)	0.5398(14)	0.5433(31)

Vicanicin

Preparation of Bromoacetylvicanicin. Thionyl chloride (20 g) and α-bromoacetic acid (6 g, 0.04 mole) were boiled under reflux for one hour. The dark brown solution was then distilled through a 12 cm vigreux column, and the fraction that distilled at 125-130° was collected to yield 3.1 g (0.017 mole, 40%) of α-bromoacetylchloride: bp 125-130° [lit.[51] bp 127° and 130°]. Vicanicin (50 mg, 0.127 mmole) was dissolved in 20 ml of anhydrous benzene. One milliliter of α-bromoacetylchloride was added to the benzene solution, and the solution was boiled under reflux for 48 hr. The solvent was evaporated at reduced pressure, and the resulting gum was crystallized from chloroform-cyclohexane (*ca.* 1:1) to yield 35 mg (0.070 mmole, 55%) of bromoacetylvicanicin: mp 176.5-179°; mass spectrum (70 eV) *m/e* (rel obsd intensity, calcd intensity) 508 (0.055, 0.030), 506 (0.222, 0.214), 504 (0.445, 0.469), 502 M^+ (0.278, 0.288), 480 (0.089, 0.030), 478

(0.222, 0.214), 476 (0.423, 0.469), 474 (0.293, 0.288), 471 (0.144, 0.122), 469 (0.490, 0.497), 467 (0.366, 0.381).

Preparation of *O*-Ethylvicanicin 26. Excess diazoethane in ether was added to a solution of vicanicin (103 mg, 0.27 mmole) in ten milliliters of ether-ethanol (1:1). The slightly yellow solution was allowed to stand at room temperature for 48 hr. The solvent was evaporated at reduced pressure to yield a gum that was crystallized from benzene-high boiling petroleum ether to yield 36 mg of 26. Several crops of 26 were combined to yield 101 mg (0.24 mmole, 89%): mp 185-186.5° [lit.[16] mp 185-186°]; nmr ($DCCl_3$) τ 8.57 (t, 3, J = 7 Hz), 7.70 (s, 3), 7.56 (s, 3), 7.51 (s, 6), 6.25 (s, 3), and 6.00 (q, 2, J = 7 Hz).

Preparation of Methyl-*O*-ethylvicanicate 27. A solution 28 (100 mg, 0.24 mmole) in 20 ml of methanol was treated with 200 mg of freshly cut sodium under reflux. The reaction was boiled under reflux for an additional hour. After cooling the solution to *ca.* 5°, cold dilute hydrochloric acid was added to *p*H 2. The acidic solution was extracted with 50 ml of ether. After the ether was washed with 20 ml of cold 1*N* hydrochloric acid, the solution was dried, and the ether was evaporated. The residue was dissolved in a minimum amount of methanol, and the solution was allowed to evaporate slowly. After several unsuccessful attempts to crystallize this material, the crude product was dried to yield 82 mg of 27. The sample of 27 gave one spot by tlc at Rf 0.40 using benzene as the solvent.

Oxidation of Methyl-*O*-ethylvicanicate 27. A sample of the methyl-*O*-ethylvicanicate (82 mg, *ca.* 0.19 mmole) preparation was dissolved in ten milliliters of distilled glacial acetic acid. To this solution 0.5 ml of concentrated nitric acid was added. After 15 min, 50 ml of water was added to the deep orange solution, and the solution was extracted with four 25 ml portions of ether. The ether extracts were combined and washed repeatedly with 15 ml portions of 5 per cent sodium bicarbonate solution. The initial extracts were colorless; then they became purple colored. These purple colored extracts were combined and immediately acidified with cold hydrochloric acid.

The ether solution that had been extracted with the sodium bicarbonate solutions was extracted with three 25 ml portions of 10 per cent sodium hydroxide solution. The sodium hydroxide extracts were combined and acidified to *p*H 2 with 2*N* hydrochloric acid. The acidic solution was extracted with two 50 ml portions of ether; the combined extracts were dried and evaporated to yield 20 mg (0.081 mmole, 42%) of phenolic ester 28: mp 63-65°; nmr ($DCCl_3$) τ 8.55 (t, 3, J = 7 Hz), 7.80 (s, 3), 7.40 (s, 3), 6.02 (s, 3), 5.98 (q, 2, J = 7 Hz), and -1.30 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 260(20), 258 M^+(60), 228(32), 226(91), 199(20), 198(30), 184(56), 182(100), 172(26), 171(24), 170(84), 169(44).

The sodium bicarbonate extracts from above that had been acidified were extracted with two 25 ml portions of ether. After the ether was dried, it was evaporated at reduced pressure to yield an orange colored oil. This oil was crystallized from *n*-hexane to yield 10 mg

(0.059 mmole, 31%) of an orange quinone 29: mp 126-127°; mass spectrum (70 eV) *m/e* (rel intensity) 188(32), 186 M^+(100), 160(17), 158(52), 130(20), 123(64), 103(33), 95(80), 83(68); emd M^+ 186.0113 (80) ($C_8H_7ClO_3$ 186.0083).

Oxidation of Methyl-*O*-methylvicanicate 32. A sample of 31 prepared by Balthis[23] was recrystallized from methanol to yield colorless needles: mp 155-156.5° [lit.[16] mp 155-156°]. A solution of 31 (395 mg, 0.945 mmole) in ten milliliters of distilled glacial acetic acid was cooled to *ca.* 10°. Concentrated nitric acid (0.5 ml) was added, and the orange solution was swirlled for 15 min. After the acidic solution was diluted with 100 ml of water, the solution was extracted with five 30 ml portions of ether. The combined ether extracts were extracted with four 20 ml portions of 5 per cent sodium bicarbonate solution. The first two extracts were colorless and were discarded; the last two extracts were purple. The purple extracts were immediately acidified with cold 3*N* hydrochloric acid, and the acid solution was extracted with three 20 ml portions of low boiling petroleum ether. The combined extracts were dried, and the solvent was evaporated to yield an orange semicrystalline compound (58 mg). The orange material was recrystallized from *n*-hexane to yield 40 mg (0.23 mmole, 24%) of an orange quinone 35 mp 126-127°; mmp with 43 126-127°; mass spectrum (70 eV) *m/e* (rel intensity) 188(30), 186 M^+ (100), 160(19), 158(52), 130(17), 123(60), 103(38), 95(75), 83(80); emd M^+ 186.0051(80), ($C_8H_7ClO_3$ 186.0083).

The ether extracts above that were extracted with sodium bicarbonate solution were also extracted with three 20 ml portions of 20 per cent aqueous sodium hydroxide. The basic extracts were combined and acidified with cold concentrated hydrochloric acid. After the acidic solution was extracted with three 30 ml portions of ether, the ether extracts were combined and dried. Evaporation of the solvent yielded a crystalline solid. Recrystallization of this solid from methanol-water (2:1) yielded 127 mg (0.520 mmole, 55%) of colorless crystals 33: mp 77-78° [lit.[16] mp 77-78°]; nmr ($DCCl_3$) τ 7.85 (s, 3), 7.41 (s, 3), 6.18 (s, 3), 6.04 (s, 3), and -1.40 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 246(23), 244 M^+(72), 214 (47), 213(47), 212(100), 186(26), 185(19), 184(76), 183(24), 182(39), 171(9), 169(26), 143(7), 141(18); ir (KBr) 3405, 2950, 1655, 1600, 1560, 1445 k among others.

A sample of the phenolic ester was treated with an excess of ethereal diazomethane. After 24 hr the solvent was evaporated, and the solid sample, (34) mp 52-59°, was dissolved in deuterochloroform: nmr ($DCCl_3$) τ 7.82 (s, 3), 7.78 (s, 3), 6.29 (s, 3), 6.23 (s, 3), and 6.14 (s, 3): mass spectrum (70 eV) *m/e* (rel intensity) 260(20), 258 M^+(59), 229(45), 228(31), 227(100), 226(51), 183(26); ir (film) 2950, 2860, 1735, 1590, 1560, 1450 k among others; glpc (1/8 in. x 12 ft., 3% OV-17), R_t 11.0 min, ct 160-260°, lpr 10° min^{-1}, nfr 70% at 80 psig.

Preparation of 3,5-dimethoxytoluene 38. One mole (23 g) of freshly cut sodium was slowly added to a solution of 3,5-dihydroxy-

toluene (52.1 g, 0.365 mole) in 300 ml of methanol. The dark colored solution was boiled under reflux while a slow stream of nitrogen was passed through the reaction vessel. The solution was then stirred under reflux while dimethyl sulfate (100 g, 0.79 mole) was added. The colorless reaction mixture was slightly acidic to *p*H paper. Upon the addition of 15 ml of 30 per cent sodium hydroxide solution, the reaction mixture became dark colored and more dimethyl sulfate (50 g, 0.40 mole) was added. This alternate addition of dimethyl sulfate and sodium hydroxide solution was continued until a total of 200 g (1.60 mole) of dimethyl sulfate was added. The solution was made strongly basic with sodium hydroxide solution and was then extracted with four 200 ml portions of ether. The ether extracts were combined and washed with 100 ml of 15 per cent sodium hydroxide and 100 ml of water. After the solution was dried, the ether was removed by distillation. The residue was distilled *in vacuo* and the fraction boiling at 95-98° (6 mm) [lit.[52] bp 110-112° (17 mm)] was collected to yield 43.18 g (0.284 mole, 78%) of 38: nmr (neat) τ 7.80 (s, 3), 6.45 (s, 6), and 3.70 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 152 M^+(100), 123(78), 122(22), 121(28), 109(78), and 108(25); glpc (1/8 in. x 12 ft., 3% OV-17), R_t 5.4 min, ct 150-230°, lpr 10° min^{-1}, nfr 70% at 80 psig.

Preparation of 2,6-dimethoxy-*p*-xylene 39. A solution of 2.25*M* *n*-butyllithium (*ca.* 0.56 mole) in 250 ml of *n*-hexane was slowly added to 43.18 g (0.284 mole) of 38 dissolved in 150 ml of ether. The mixture was boiled under reflux for ten hours and then cooled to 0°. A cold solution of dimethyl sulfate (100 g, 0.803 mole) in 100 ml of anhydrous

ether was slowly and cautiously added to the stirred reaction mixture. The mixture was boiled under reflux for 1.5 hr. The reaction mixture was washed with two 200 ml portions of water, 100 ml of 5 per cent sodium bicarbonate solution, and 100 ml of water. The solution was dried, and the hexane and ether were removed by distillation. The remaining material was distilled *in vacuo*, and the fraction boiling at 80-90° (1.5 mm) was collected to yield 36.14 g of pale yellow liquid. This material was dissolved in methanol; crystals were deposited upon cooling to yield 28.82 g (0.174 mole, 61%) of 39: mp 46-48°; nmr ($DCCl_3$) τ 7.82 (s, 3), 7.75 (s, 3), 6.42 (s, 6), and 3.75 (s, 2); glpc (1/8 in. x 12 ft, 3% OV-17), R_t 4.9 min, ct 160-230°, 1pr 10° min^{-1}, nfr 70% at 80 psig; mass spectrum (70 eV) *m/e* (rel intensity), 166 M^+ (100), 151(26), 135(21), 121(18), 105(20), 91(27).

Preparation of 2,6-Dichloro-3,5-dimethoxy-*p*-xylene 41. Five milligrams of ferric chloride was added to a solution of 39 (20.82 g, 0.125 mole) in 275 ml of benzene. This mixture was cooled to *ca.* 10°, and chlorine was bubbled through the cooled solution for 20 min. The reaction mixture was flushed with nitrogen for 30 min and then extracted with portions of 10 per cent aqueous sodium bisulfite until no reaction occurred. The benzene solution was washed with two 50 ml portions of water. After drying the solution, the solvent was evaporated to yield a yellow oil. This oil was dissolved in a minimum amount of 95 per cent ethanol and cooled to *ca.* -50°; crystallization occurred. The mixture was warmed to room temperature and the crystals were collected by filtration. Several crops of crystals were collected

in the same manner and the combined material was air dried to yield 23.73 g (0.10 mole, 80%) of 41: mp 58-61°; mass spectrum (70 eV) *m/e* (rel intensity), 238(10), 236(64), 234 M^+(100), 221(14), 219(21), 190(45), 188(65), 175(25), 173(86); emd M^+ 234.0224(76) ($C_{10}H_{12}Cl_2O_2$ 234.0213); glpc (1/8 in. x 12 ft., 3% OV-17), R_t 5.2 min, ct 160-250°, lpr 10° min^{-1}, nfr 65% at 80 psig; nmr ($DCCl_3$) τ 7.76 (s, 3), 7.52 (s, 3), and 6.22 (s, 6):

Preparation of 5-Chloro-2,4-dimethoxy-3,6-dimethylbenzoic acid 42. A solution of 41 (12.54 g, 0.053 mole) in 150 ml of anhydrous ether was added dropwise to a stirred solution of 100 ml of *n*-butyllithium (*ca.* 0.225 moles) in *n*-hexane and 100 ml of anhydrous ether. The solution was boiled under reflux for one hour and then cooled to *ca.* 0°. Carbon dioxide, dried over 3 Å molecular sieves, was passed over the surface of the solution, with rapid stirring, for a period of four hours. The solution was diluted with 100 ml of water and acidified to *ca. p*H 3 using hydrochloric acid. The acidic solution was extracted with two 200 ml portions of ether. The ether extracts were combined and extracted with three 100 ml portions of 5 per cent sodium bicarbonate solution. The aqueous bicarbonate solutions were combined, acidified to *p*H 3, and extracted with two 100 ml portions of ether. After drying the solution, the ether was evaporated to yield 12.35 g of a yellow oil. The oil crystallized upon standing and was recrystallized from isopropyl ether-high boiling petroleum ether (*ca.* 1:10). Several crops of the pale yellow crystals were collected to yield 8.10 g (0.033 mole, 62%) of 42: mp 86-88°;

nmr ($DCCl_3$) τ 7.71 (s, 3), 7.54 (s, 3), 6.13 (s, 6), and -0.03 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity), 246(33), 244 M^+(100), 229(15), 228(35), 227(35), 226(89), 185(8), 183(26).

Preparation of Methyl 5-chloro-2,4-dimethoxy 3,6-dimethylbenzoate 36. One gram (0.0041 mole) of 42 was dissolved in ten milliliters of ether. An excess of ethereal diazomethane was added to this solution. The yellow solution was allowed to stand for eight hours. The ether was evaporated to yield 982 mg (3.8 mmole, 93%) of 36: mp 54-58.5°; nmr ($DCCl_3$) τ 7.78 (s, 3), 7.71 (s, 3), 6.26 (s, 3), 6.21 (s, 3), and 6.10 (s, 3); mass spectrum (70 eV) *m/e* (rel intensity) 260(20), 258 M^+(60), 229(36), 228(33), 227(100), 226(51), 180(26); ir (film) 2980, 2930, 2840, 1730, 1590, 1565 cm^{-1} among others; glpc (1/8 in. x 12 ft, 3% OV-17), R_t 11.0 min, ct 160-260°, 1pr 10° min^{-1}, nfr 70% at 80 psig.

Synthesis of 3-Chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone 43.[12] Boron trifluoride etherate (3 ml) was added to a solution of 2,5-dimethyl-*p*-benzoquinone (10 g, 0.074 mole) in 60 ml of distilled acetic anhydride, and the solution was allowed to stand at room temperature for five hours. The solution was then cooled to 0°, and 600 ml of distilled water was added. The crystalline precipitate that formed was collected and washed thoroughly with water to yield 16 g of crude damp material. The crude material was recrystallized from methanol-water (*ca.* 4:1) to yield 12.06 g (0.0431 mole, 58%) of 1,4-dimethyl-2,3,5-triacetoxybenzene: mp 107.5-109.5° [lit.[53] mp 105-107°].

Three grams (0.011 mole) of 1,4-dimethyl-2,3,5-triacetoxybenzene was dissolved in 50 ml of 95 per cent ethanol, and chlorine was bubbled through the solution for 1.5 hr. The solution was flushed with nitrogen for 30 min; then the solution was reduced in volume to ten milliliters. The chlorinated product was vigorously shaken with three 50 ml portions of 2*N* sodium hydroxide solution. The basic fraction was acidified with 4*N* hydrochloric acid and extracted with three 50 ml portions of ether. The ether solution was extracted with three 50 ml portions of saturated sodium bicarbonate solution, and the sodium bicarbonate layer was acidified with 4*N* hydrochloric acid. The acidic layer was extracted with three 50 ml portions of ether; the ether was dried and evaporated to give a dark brown oil. This oil was chromatographed over a silica acid column (1 cm x 10 cm) by eluting with high boiling petroleum ether-chloroform (4:1). The first fraction to be eluted from the column was evaporated to dryness and crystallized from high boiling petroleum ether to yield 201 mg (1.08 mmole, 10%) of orange crystals: mp 126-128°; mmp with 35 126-128°; mass spectrum (70 eV) *m/e* (rel intensity) 188(39), 186 M^+(100), 160(17), 158(50), 130(20), 123(60), 103(33), 95(89), 83(68). The R_f values of 35 and 3-chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone were identical by tlc in four different solvent systems.

Preparation of Methyl *O,O'*-dimethylvicanicate 50. Methyl-*O*-methylvicanicate (78 mg, 0.18 mmoles) was dissolved in five milliliters of methanol and five milliliters of ether. This solution was treated with an excess of ethereal diazomethane and was allowed to stand at room

temperature for 48 hr. The solvent was evaporated to yield a colorless oil that crystallized from methanol-ether (*ca.* 3:1) to yield 64 mg (0.146 mmole, 81%) of 50: mp soften 86° melt 94-97° [lit.[16] mp 97-98°]; mass spectrum (70 eV) *m/e* (rel intensity), 444(71), 443(25), 442 M^+(100), 217(12), 215(36); nmr ($DCCl_3$) τ 7.82, 7.80, 7.77, 7.73 (unresolved singlets, 12), 6.67 (s, 3), 6.53 (s, 3), 6.23 (s, 3), and 6.20 (s, 3).

Oxidation of Methyl *O,O'*-dimethylvicanicate 50. A sample of 50 (20 mg, 0.045 mmoles) was dissolved in two milliliters of distilled glacial acetic acid and treated for with 0.25 ml of concentrated nitric acid. After 15 min, 15 ml of water was added and the acidic solution was extracted with five five milliliter portion of ether. The combined ether extracts were extracted with five two milliliter portions of 5 per cent sodium bicarbonate solution and five two milliliters portions of 10 per cent sodium hydroxide solution. Both the bicarbonate and sodium hydroxide extracts were acidified with concentrated hydrochloric acid, and the acidic solutions were extracted with ether. Evaporation of the ether extracts from both solutions showed no material.

The original ether extracts were dried and evaporated to yield 17 mg (0.039 mmole, 85%) of 50: mp 94-96° [lit.[16] mp 97-98].

CHAPTER III

DISCUSSION

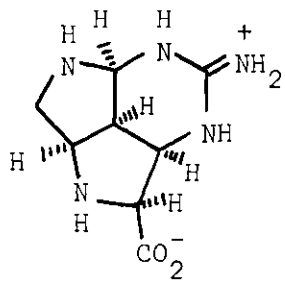
The Crystal Structure of Viocidic Acid

The antibiotic viomycin is a peptide that yields, upon acid hydrolysis, the amino acids L-serine, L-α,β-diaminopropionic acid, L-β-lysine, and viomycidine, as well as small amounts of peptides, carbon dioxide, ammonia, and urea. One of the components isolated from the hydrolysate by ion exchange chromatography on Dowex 50(H^+) was purified, converted to the dihydrobromide salt, and crystallized. The order of elution from the ion exchange column indicated that this compound was more basic than viomycidine. The nmr spectrum of this compound was complicated and could not be interpreted. This material gave positive ninhydrin and Weber tests. Analysis by tlc showed that viomycidine and DAPA were not produced by acid hydrolysis of this material. The purpose of this research was to determine the structure of this compound. Single crystal X-ray diffraction was the method of choice since only a small amount of the pure material was available (*ca.* 10 mg).

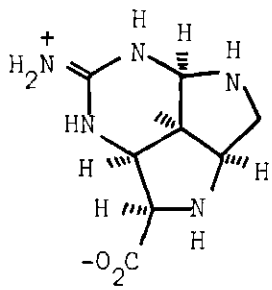
The unit cell dimension of this compound obtained from X-ray precession photographs were within experimental error of the dimensions of the compound viocidic acid (6). Johnson reported the structure of viocidic acid, from X-ray diffraction studies, to be 6 (rather than 6'); however bond angles and lengths were not reported. The assignment

of atomic numbers to the light atoms in 6 were not explained, and the mode of formation of 6 from viomycin was not discussed. Hence, a more exact determination of the structure was desired.

The structure determined for viocidic acid during the course of this research by X-ray diffraction techniques was 2,5,8,10-tetraaza-9-iminotricyclo[5.3.1.$0^{4,11}$]undecane-6-carboxylic acid (6). A view of the viocidic acid cation is shown in Figure 1.[54]



6



6'

Table 7 lists the bond lengths and bond angles with their estimated standard deviations. All bond lengths are within two standard deviations of commonly accepted values. The trend toward slightly longer bond lengths in the five membered rings may represent real values longer than the accepted carbon-carbon bond length of 1.536 Å for ethane. It has been postulated that nonbonded steric repulsion may cause an extension of 0.02 Å for highly substituted sp^3 carbon-carbon bonds.[55]

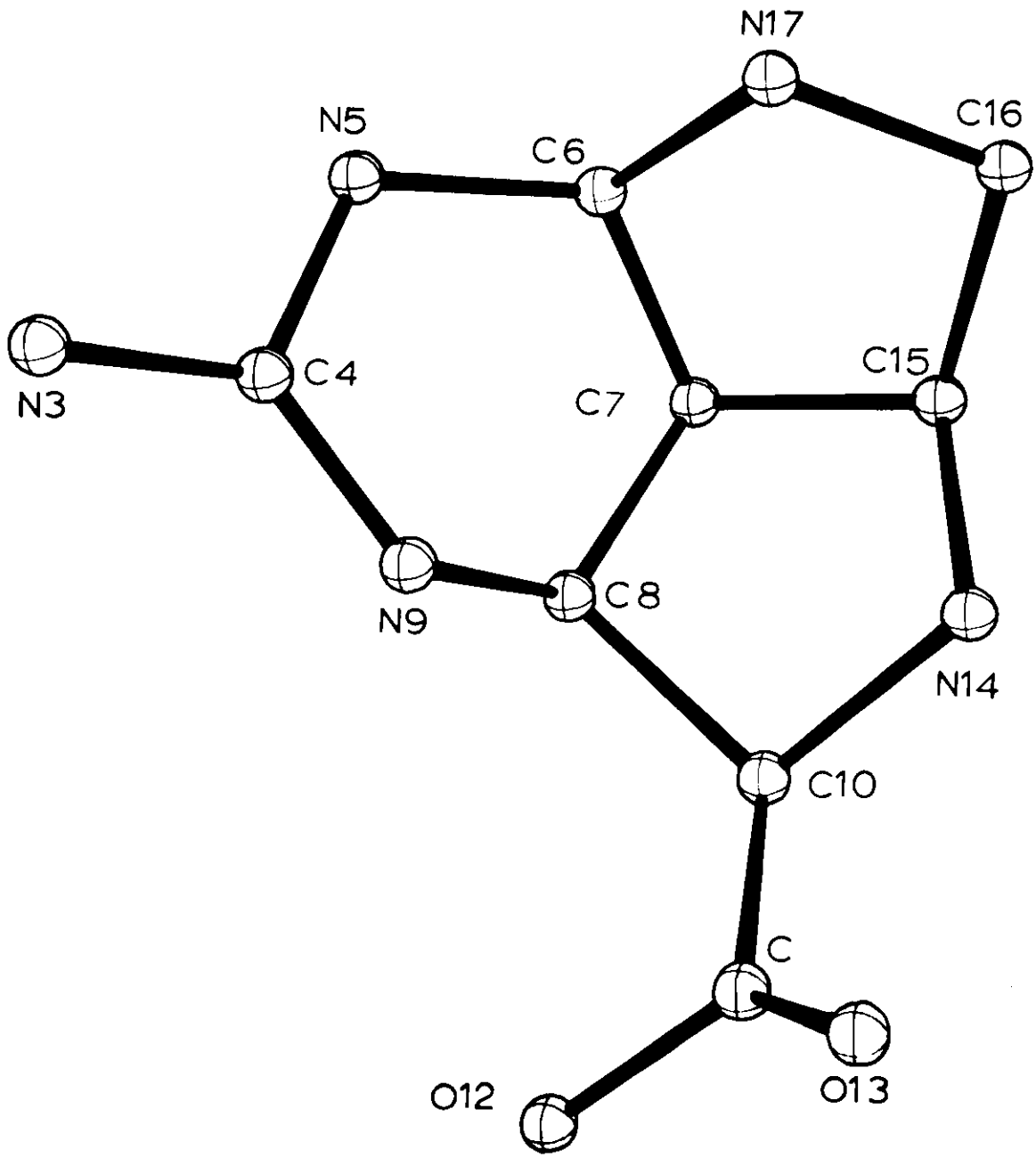


Figure 1. Viocidic Acid Cation

Table 7. Bond Lengths and Bond Angles in the Viocidic Acid Cation

Bond Length		Bond Angles	
Atoms	Length(Å)	Atoms	Angle(°)
N(3)-C(4)	1.30(3)	N(5)-C(4)-N(9)	119(2)
C(4)-N(5)	1.33(3)	N(3)-C(4)-N(5)	117(2)
N(5)-C(6)	1.47(3)	C(4)-N(5)-C(6)	119(2)
C(6)-C(7)	1.51(3)	N(5)-C(6)-C(17)	104(2)
C(7)-C(8)	1.50(3)	N(5)-C(6)-C(7)	119(2)
C(8)-N(9)	1.49(3)	C(6)-C(7)-C(8)	113(2)
N(9)-C(4)	1.33(3)	N(3)-C(4)-N(9)	123(2)
C(18)-C(10)	1.56(3)	C(7)-C(8)-N(9)	114(2)
C(10)-C(11)	1.52(3)	C(8)-N(9)-C(4)	121(2)
C(11)-O(12)	1.30(3)	N(9)-C(8)-C(10)	110(2)
C(11)-O(13)	1.20(3)	C(7)-C(8)-C(10)	106(2)
C(10)-N(14)	1.58(3)	C(8)-C(10)-N(14)	101(2)
N(14)-C(15)	1.51(3)	C(10)-N(14)-C(15)	108(2)
C(15)-C(7)	1.62(3)	C(8)-C(10)-C(11)	122(2)
C(15)-C(16)	1.52(3)	N(14)-C(10)-C(11)	106(2)
C(16)-N(17)	1.48(3)	C(10)-C(11)-O(12)	108(2)
N(17)-C(6)	1.62(3)	C(10)-C(11)-O(13)	124(2)
		O(13)-C(11)-O(12)	127(2)
		N(14)-C(15)-C(16)	116(2)
		N(14)-C(15)-C(7)	103(2)
		C(7)-C(15)-C(16)	110(2)
		C(15)-C(7)-C(8)	107(2)
		C(15)-C(7)-C(6)	102(2)
		C(15)-C(16)-N(17)	104(2)
		C(16)-N(17)-C(6)	105(2)
		N(17)-C(6)-C(7)	107(2)

Table 8 gives the least-squares plane[56] through atoms N(3), C(4), N(5), and N(9). These atoms would be expected to be planar. All these atoms are within ± 0.04 Å of the plane. The bond angles around the central atom [C(4)] are within one standard deviation of 120°.

Table 8. Least Squares Plane of the Guanidino Cation in Viocidic Acid: 0.55082X + 0.41941Y + 0.72159Z - 5.44737 = 0 [56]

Atom	Distance from Plane (Å)
N(3)	-0.01516
C(4)	0.04035
N(5)	-0.01345
N(9)	-0.01174

Table 9 gives the least-squares plane through atoms C(10), C(11), O(12), and O(13). All these atoms are within ± 0.04 Å of the plane.

Table 9. Least Squares Plane of the Carboxylate Anion and the α Carbon in Viocidic Acid: 0.81248X + 0.18746Y - 0.55203Z - 5.18595 = 0 [56]

Atom	Distance from Plane (Å)
C(10)	-0.01201
C(11)	0.04358
O(12)	-0.01290
O(13)	-0.01867

The assignment of oxygen atoms was obvious since the geometry of the atoms C(11), O(12), and O(13) suggested a carboxylate anion. The oxygen atoms of the three water molecules were not within reasonable bonding distance to any other atoms.

The assignment of the nitrogen atoms of the guanidino function was obvious from the bond lengths and bond angles. The thermal parameters of an atom theoretically will correct the scattering power (expressed in electrons) of the atom for the decrease in electron density due to thermal motion. These thermal parameters also correct the scattering power of an atom assigned an incorrect number of electrons (*i.e.* nitrogen assigned as a carbon) by spreading the electrons over a larger volume (decrease the electron density) or concentrating the electrons into a small volume (increasing the electron density). For example, the thermal parameters of a carbon atom that is assigned scattering factors for nitrogen will decrease the scattering power of the nitrogen atom by spreading the electrons over a larger volume (large thermal parameter). Although these arguments are not rigorous, they give some indication as to whether the assignment of the atomic number is correct.

Table 10 is a list of the isotropic thermal parameters for two cases: (1) all the carbon and nitrogen atoms were assigned scattering factors of carbon; (2) all the carbon and nitrogen atoms were assigned scattering factors of nitrogen. In Table 10 two atoms [N(14) and N(17)] were found in the list for case (2) that have thermal parameters about the same value as the thermal parameters of known nitrogen atoms N(5) and N(9). The assignment of these atoms [N(14) and N(17)] as nitrogens was substantiated by the value of their thermal parameters in case (1). In this case, atoms N(14) and N(17) have temperature factors considerably smaller than those of known carbon atoms. The temperature factor

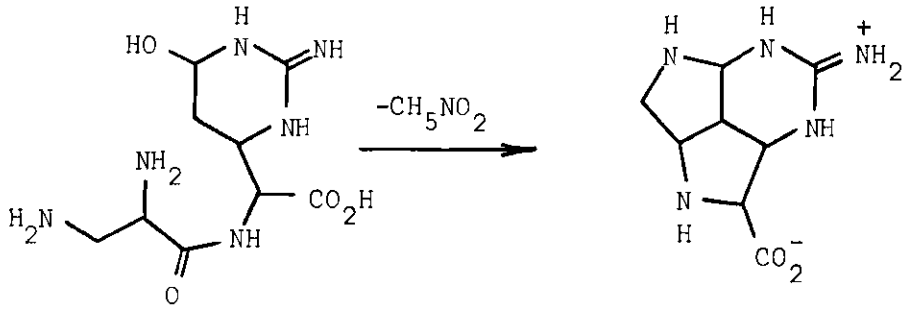
for atom N(3) does not agree as well as the other nitrogen atoms; however, this may be an indication of the greater freedom this atom has with respect to other nitrogens in the rings.

Table 10. Isotropic Thermal Parameters: All Carbons, All Nitrogens

Atom	B (All Nitrogen)	B (All Carbon)
N(3)	2.496	1.580
C(4)	2.953	1.765
N(5)	1.746	0.746
C(6)	4.446	2.388
C(7)	2.951	1.516
C(8)	3.293	1.916
N(9)	1.132	0.240
C(10)	2.968	1.479
C(11)	3.907	2.704
N(14)	1.396	0.775
C(15)	2.695	1.475
C(16)	3.378	1.919
N(17)	1.081	0.408

The absolute configuration of viocidic acid was determined by Hamilton's significance test to be that of 6. The structure determined for viocidic acid in the course of this research was identical with the structure proposed by Johnson, *et al*. However, the data were refined to an R_1 value lower than that reported by Johnson (0.090 *vs.* 0.121).

One of the peptides formed by partial acid hydrolysis of viomycin was the diaminopropionylviomycidine precursor 23.[57] It may be reasonable to assume that this peptide is the precursor of viocidic acid 6.



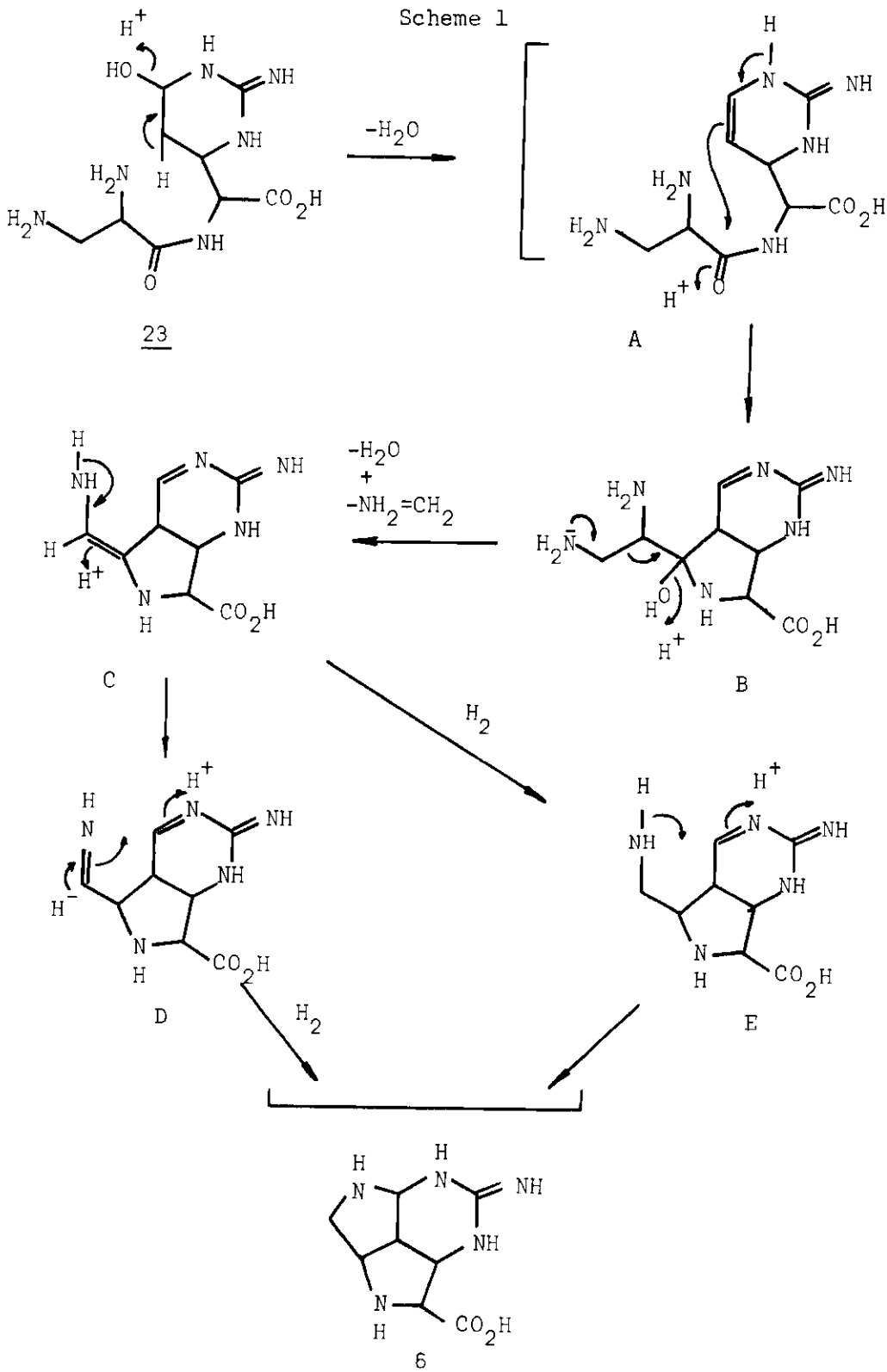
$C_9H_{18}N_6O_4$ $C_8H_{13}N_5O_2$

23 6

A mechanism that appears reasonable for this conversion, when the extremely low yields are considered, is shown in Scheme I.[58]

Compound 23 could readily lose water under the strongly acidic conditions to give A. The enamine A could then attack the protonated amide carbonyl group of the diaminopropionyl residue to yield intermediate B. Intermediate B could then undergo a retro Mannich reaction; loss of $H_2\overset{+}{N} = CH_2$ and water would yield intermediate C. Intermediate C could either undergo a proton shift to yield D, and D could be reductively cyclized to viocidic acid 6 or intermediate C could be reduced to intermediate E and then undergo cyclization to viocidic acid 6. The appropriate compound could be reduced by formaldehyde, ammonia or other reducing agents in the hydrolysis medium. When considering this mechanism one should realize that the product is isolated in less than 0.5 per cent yield.[6] There is also the possibility that viocidic acid results from hydrolysis of a minor component present in commercial viomycin.[6]

Scheme 1



The Structure of 2-(2,3-Dichloro-2-Pyrrolin-1-yl)-1-pyrroline (24)

The product reported for the reaction of 2-pyrrolidinone with hydrogen chloride and phosphorous pentachloride followed by treatment with base was 2-chloro-Δ^1-pyrroline (8). Preliminary investigations of the spectroscopic properties indicated the proposed structure was incorrect. The purpose of this research was to determine the structure of the product (24) and to investigate the chemistry of this product.

The compound 24 was prepared as described by Tafel and Wassmuth, but was purified by sublimation to yield colorless crystals (mp 50-51°). The mass spectrum of 24 showed a molecular ion at *m/e* 204.029, which indicated the molecular formula $C_8H_{10}N_2Cl_2$. This formula also satisfied the elemental analyses. The nmr spectrum of 24 at 60 MHz and spin decoupling experiments at 100 MHz indicated that the structure for 24 contained $-CH_2CH_2-$ and $-CH_2CH_2CH_2-$ groups.

The compound was easily oxidized by neutral potassium permanganate, and did not contain a labile chlorine since no precipitate was formed when the compound was treated with acidic silver nitrate solution. The compound was unstable; the colorless crystals became dark brown after 12 hr at room temperature. A solution of 24 in carbon tetrachloride began to precipitate a brown oil in one hour at room temperature.

Since the spectroscopic data and preliminary chemical investigations were not definitive, the technique of single crystal X-ray diffraction was considered as a possible approach to the problem. Several attempts were made to enclose the crystals of 24 in glass

capillaries, but the rapid decomposition and high vapor pressure of the compound at room temperature prevented data from being collected using these crystals.

Compound 24 was found to be a base that readily formed stable mineral acid salts. The hydrobromide salt (25) of 24 was prepared by passing dry hydrogen bromide through a solution of 24 in ether. The precipitate was crystallized from acetone-water to yield well formed crystalline needles. Weissenberg film data were collected from one of these crystals, but all attempts to refine the data failed. These crystals were suspected of being twinned. In addition, a slow loss of crystallinity was attributed to the loss of solvent of crystallization. After trying numerous solvent systems for crystallization of 25, the system found suitable was slow cooling of a saturated aqueous solution of 25. This yielded colorless crystalline needles that were shown to be twinned by preliminary precession photographs. However, by allowing the aqueous solution of 25 to cool slowly to form small crystals, and then allowing the solvent to slowly evaporate, large crystals (*ca.* $8 \times 4 \times 1$ mm) were formed. By proper cutting, a single crystal of appropriate size was fashioned, and precession photographs showed this crystal to be suitable for data collection.

The structure determined for 25 by X-ray diffraction techniques was (E)-2,3-Dichloro-1-(2-pyrrolidinylidene)-2-pyrrolinium bromide.[59] Perspective views of 25 are shown in Fig. 2 and Fig. 3.

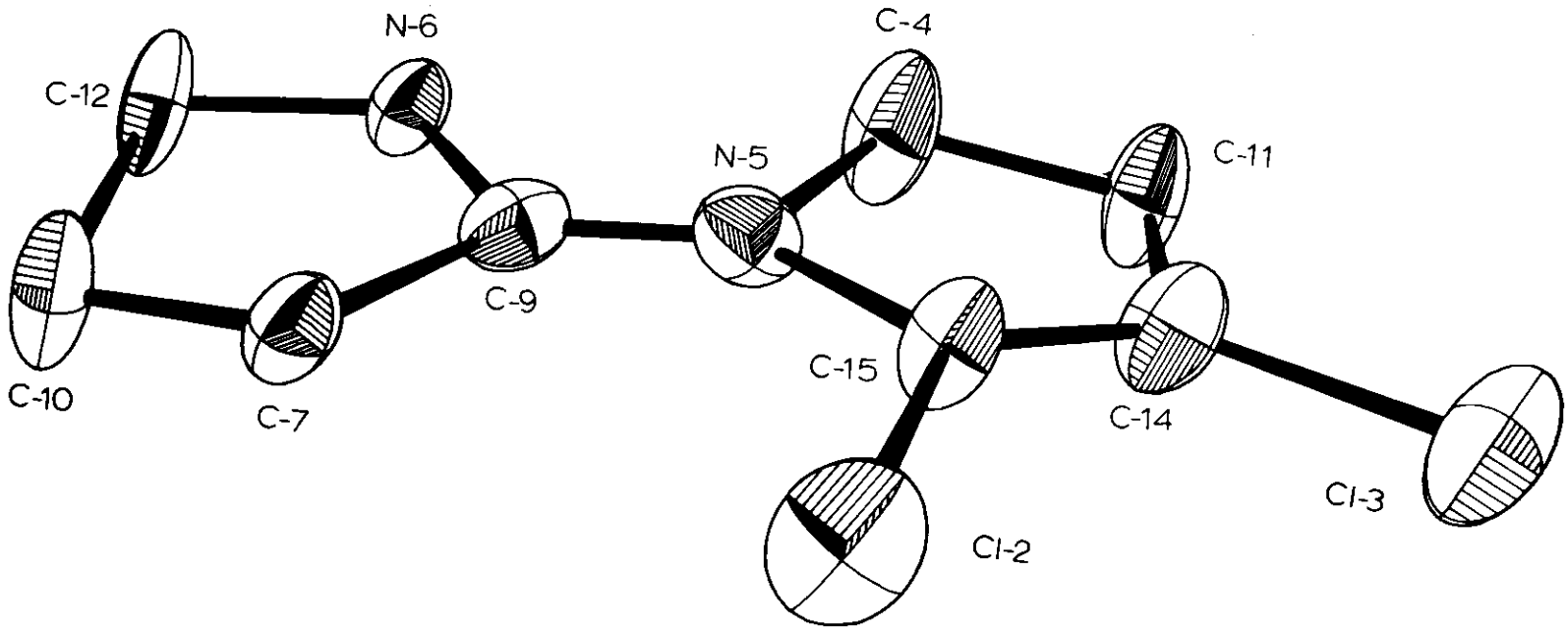


Figure 2. Perspective View of 25

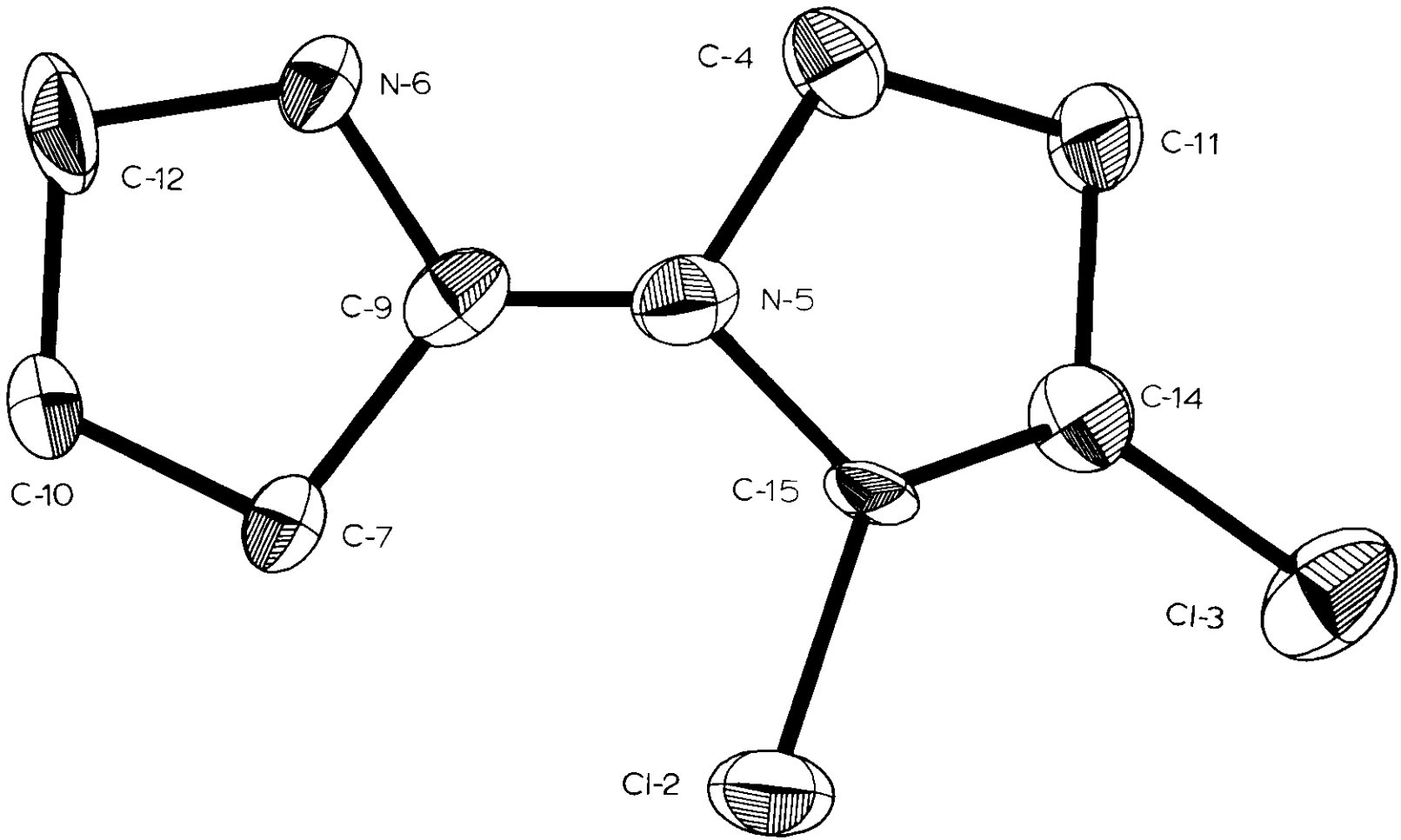


Figure 3. Planar View of 25

Table 11 lists the final anisotropic thermal parameters. These parameters are represented by the elipisoids of 50 per cent probability in Figure 2.

Table 11. Final Anisotropic Thermal Parameters for 25

Atom	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br(1)	0.0260(7)	0.0017(1)	0.0184(6)	0.0006(2)	0.0156(5)	0.0003(2)
Cl(2)	0.0249(17)	0.0018(3)	0.0116(16)	-0.0006(5)	0.0107(13)	-0.0009(4)
Cl(3)	0.0251(19)	0.0015(3)	0.0235(20)	0.0013(5)	0.0135(15)	0.0020(5)
C(4)	0.042(10)	0.001(1)	0.020(8)	0.002(2)	0.022(7)	0.000(2)
N(5)	0.015(6)	0.002(1)	0.013(5)	0.000(2)	0.010(4)	0.000(2)
N(6)	0.017(5)	0.001(1)	0.014(5)	0.001(1)	0.011(4)	0.001(1)
C(7)	0.027(7)	0.001(1)	0.016(6)	0.001(2)	0.016(6)	-0.001(2)
O(8)	0.033(5)	0.002(1)	0.015(4)	-0.002(1)	0.018(4)	-0.001(1)
C(9)	0.0116(6)	0.001(1)	0.013(6)	0.000(2)	0.007(5)	0.001(2)
C(10)	0.035(8)	0.000(1)	0.025(8)	0.000(2)	0.022(7)	0.000(1)
C(11)	0.0291(7)	0.001(1)	0.017(7)	0.002(2)	0.015(6)	0.000(2)
C(12)	0.030(8)	0.001(1)	0.027(8)	0.000(2)	0.019(7)	-0.002(2)
O(13)	0.030(5)	0.001(1)	0.019(5)	-0.001(1)	0.014(4)	0.000(1)
C(14)	0.022(7)	0.001(1)	0.017(7)	-0.001(2)	0.012(5)	-0.001(2)
C(15)	0.022(7)	0.001(1)	0.007(5)	-0.000(2)	0.008(5)	-0.001(2)

Table 12 lists the bond lengths and bond angles with their estimated standard deviations. All bond lengths are within two standard deviations of commonly accepted values. Some of the bond lengths in the five-membered rings are slightly longer than normal values for C-C bonds, but these distances are consistent with the slightly longer bond distances typically found in strained five-membered rings.

Table 12. Final Bond Lengths and Band Angles for 25

Bond Lengths		Bond Angles	
Atom	Length(Å)	Atoms	Angle(°)
Cl(2)-C(15)	1.81(3)	Cl(2)-C(15)-C(14)	124(2)
Cl(3)-C(14)	1.83(3)	Cl(2)-C(15)-N(5)	121(2)
C(4)-N(5)	1.55(3)	Cl(3)-C(14)-C(11)	127(2)
N(4)-C(11)	1.58(3)	Cl(3)-C(14)-C(15)	124(2)
N(5)-C(15)	1.50(3)	C(15)-C(14)-C(11)	109(2)
N(5)-C(9)	1.28(3)	C(14)-C(15)-N(5)	113(2)
C(11)-C(14)	1.60(4)	C(14)-C(11)-C(4)	106(2)
C(14)-C(15)	1.24(3)	C(11)-C(4)-N(5)	102(2)
C(9)-N(6)	1.49(3)	C(4)-N(5)-C(15)	107(2)
N(6)-C(12)	1.43(3)	C(15)-N(5)-C(9)	135(2)
C(12)-C(10)	1.60(4)	C(4)-N(5)-C(9)	117(2)
C(10)-C(7)	1.60(3)	N(5)-C(9)-C(7)	121(2)
C(7)-C(9)	1.57(3)	N(5)-C(9)-N(6)	125(2)
		N(7)-C(9)-N(6)	112(2)
		C(9)-N(6)-C(12)	115(2)
		N(6)-C(12)-C(10)	101(2)
		C(12)-C(10)-C(7)	111(2)
		C(10)-C(7)-C(9)	101(2)

The molecule is nearly planar; atom C(10) is puckered slightly. Table 13 gives the least-squares plane through all the atoms in the molecule except C(10). All the atoms are within 0.06 Å of the least-squares plane except C(10), which is 0.31 Å below the plane.

The atoms N(5) and N(6) were assigned as nitrogen atoms on the basis of bond lengths and the magnitude of their isotropic thermal parameters.

Table 13. Least Squares Plane of 25 Except C(10)
0.77668X + 0.58955Y + 0.22180Z -
9.76745 = 0 [56]

Atom	Distance from Plane Å
Cl(2)	0.006
Cl(3)	0.036
C(4)	0.050
N(5)	-0.020
N(6)	0.020
C(7)	-0.040
C(9)	-0.060
C(10)	-0.310
C(11)	-0.064
C(12)	0.043
C(14)	-0.016
C(15)	0.044

Table 14 gives the isotropic thermal parameters for two cases: (1) all atoms listed were assigned the scattering power of nitrogen, and (2) all atoms listed were assigned the scattering power of carbon. Atoms N(5) and N(6) have thermal parameters that suggest the assignment as nitrogen atoms.* This assignment is confirmed by noting the bond length N(6)-C(9) is 1.49(3) Å, which agrees well with the accepted value of 1.48 Å. The bond C(9)-C(7) is 1.57(3) Å, which is more in agreement with the accepted C-C length of 1.539 Å. The bond C(9)-N(5) is 1.28(3), which is indicative of a C=N double bond.

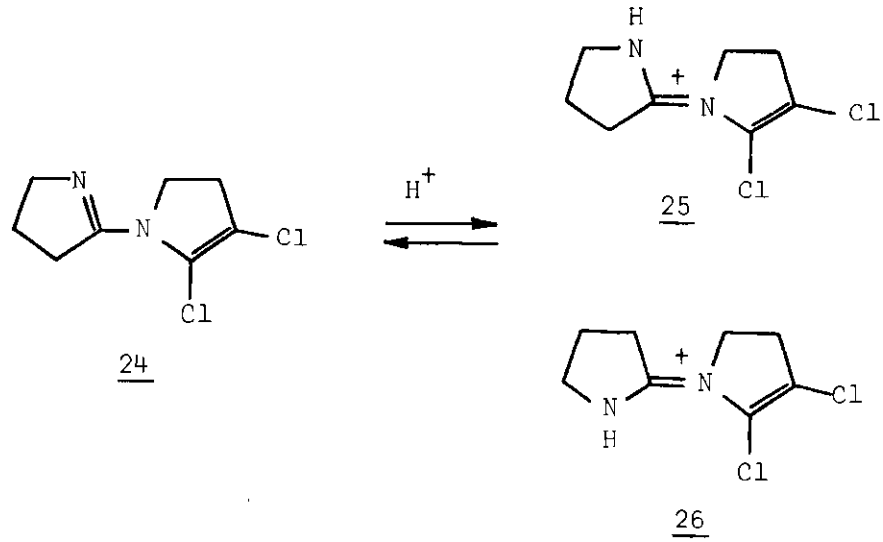
The structure of 24 can be deduced from that of 25 since 25 is a protonated form of 24. The protonation of 24 could yield two isomers

*This thesis, p 64.

Table 14. Isotropic Thermal Parameters: All Carbons, All Nitrogens

Atom	B (All Nitrogen)	B (All Carbon)
C(4)	6.24	3.53
N(5)	3.63	1.13
N(6)	1.18	-1.93
C(7)	4.90	1.70
C(9)	6.31	2.82
C(10)	6.43	3.46
C(11)	6.12	2.87
C(12)	7.51	4.62
C(14)	5.79	2.51
C(15)	7.34	3.47

in equilibrium, 25 and 26. The 100 *MHz* nmr spectrum of 24 in TFA suggest two isomers in approximately a 1:2 ratio. Apparently structure



25 crystallizes more readily than 26 since the X-ray data did not indicate any disorder resulting from a mixture of 25 and 26.

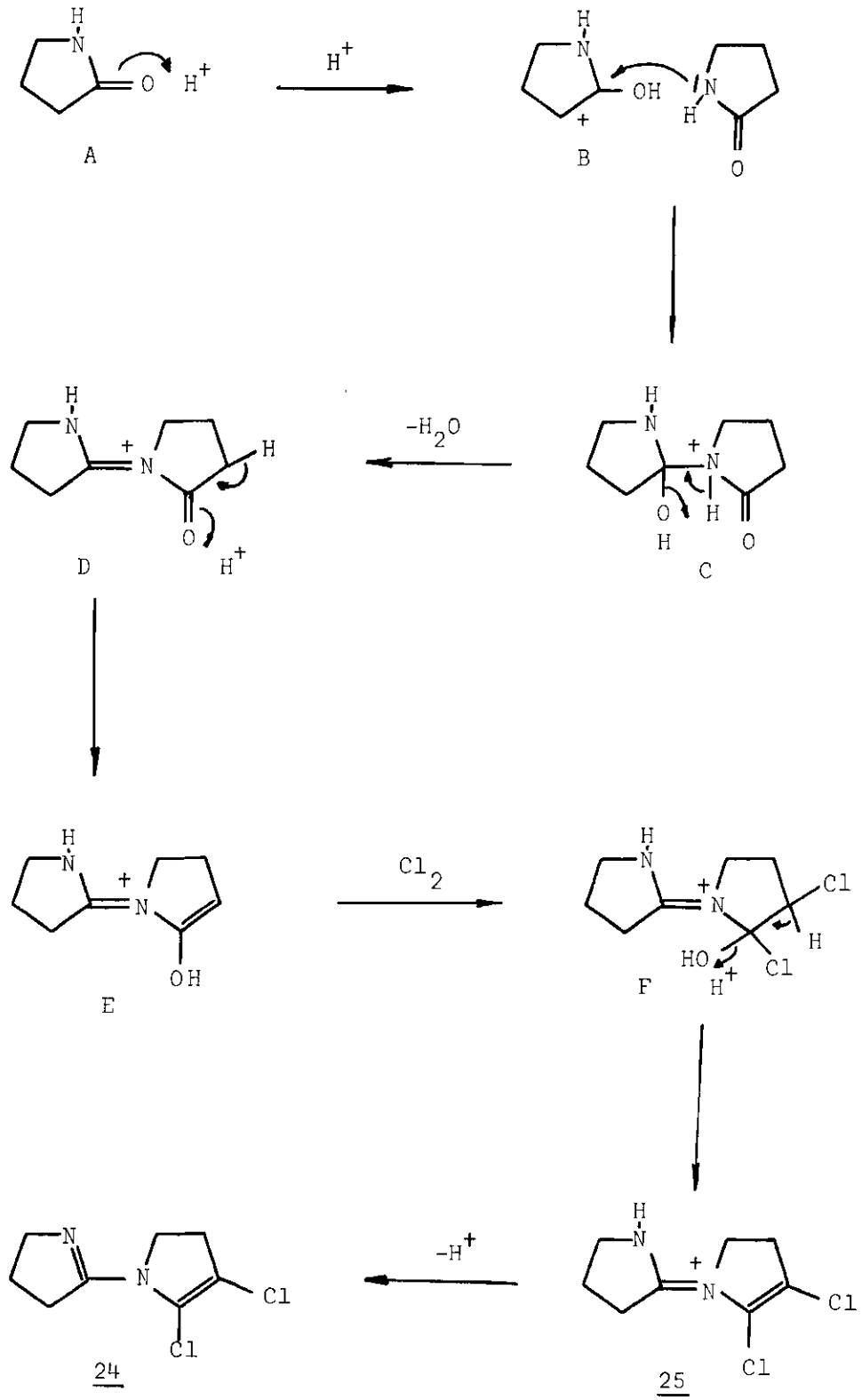
A possible mechanism for the formation of 24 is shown in Scheme 2. The strongly acidic conditions under which 24 is formed could protonate 2-pyrolidinone (A) to give B, which could be attached by unprotonated 2-pyrrolidinone to yield intermediate C. Intermediate C could be dehydrated to yield D, which could enolize to give intermediate E. Chlorine present in the reaction mixture could chlorinate the enol E to give intermediate F, which could be dehydrated to yield 25. The salt 25 when treated with strong base would yield 24.

The yield of 24 from the preparation described by Wassmuth and Taffel[11] is variable and low (*ca.* 5-20 per cent). However, when the treatment with base is omitted and the phosphate salt of 25 is isolated directly the yield (of 25) is *ca.* 50 per cent.

According to a review of *α*-chloroenamines by Viehe, *et al.*, α-chloroenamines without stabilizing electronegative β-substituents such as fluorine, chlorine, or carbonyl are hardly known.[60] However, Viehe and Buyle have prepared numerous α-chloro-β-chlorocarbonyl-enamines by treating *N,N*-substituted amides with phosgene in ether.[61] For example, when *N*-methylpyrrolidinone was treated with phosgene a 26 per cent yield of *N*-methyl-2-chloro-3-chlorocarbonyl-Δ^2-pyrroline was obtained.

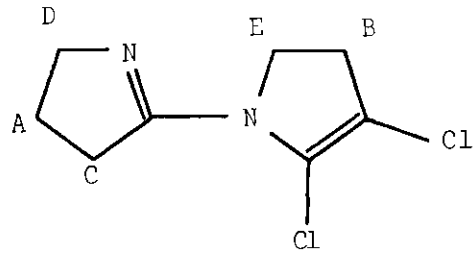
Wolf and Block[62] reported the preparation of α,β-dichloro-enamines by reacting dichloroacetylene with secondary amines. Speziale and Freeman[63] have prepared several *N,N*-dialkyl-1,2,2-tri-

Scheme 2



chlorovinylamines by treating the appropriate *N,N*-dialkyl-2,2,2-trichloroacetamides with triethyl phosphite. However, structure 24 appears to be the only example of a stable cyclic α,β-dichloroenamine.

The nmr spectrum of 24 is interpreted as shown below.

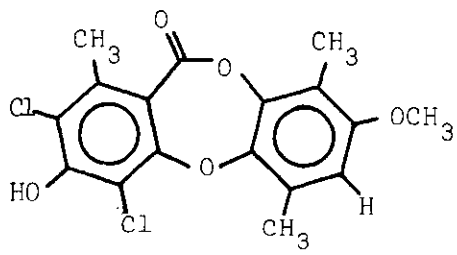


H	τ
A	8.10 m, 2. A collapses to a t, J = 8 Hz when irradiated at D, t, J = 7 Hz when irradiated at C.
B	7.30 t, 2, J = 9 Hz. B collapses to a s when irradiated at E.
C	7.10 t, 2, J = 8 Hz.
D	6.45 T, 2, J = 7 Hz.
E	6.00 t, 2, J = 9 Hz.

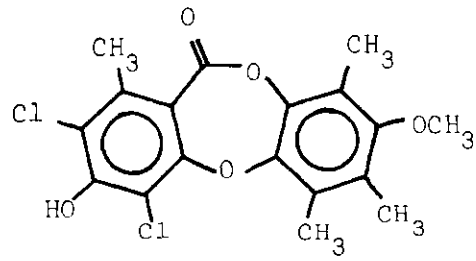
The Structure of Vicanicin

Examination of the lichens *Teloschistes flavicans*,[13] *Teloschistes flavicans Norm.*,[14] and *Teloschistes flavicans v. minor Crombie*[22] by several workers resulted in the isolation, among various anthroquinones, a colorless substance that showed mp 240-245°. Seshadri, *et al.* reported

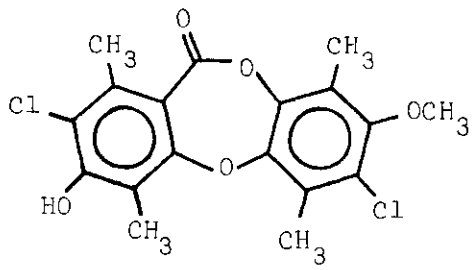
a structure (19) for the colorless substance they named vicanicin in 1962.[16] Vicanicin was characterized as a depsidone that contained two chlorine atoms, one *O*-methyl group, three *C*-methyl groups, and one hydroxyl substituent. However, later investigations of the spectroscopic properties of vicanicin indicated that it contained one additional *C*-methyl group. The structure of vicanicin was reassigned as 21 based on the assumption that the structure proposed by Seshadri was correct in all respects except the substitution of a methyl group at the only unsubstituted position (C-6). In 1968, Baillie reviewed the degradation of vicanicin and showed that although vicanicin was a depsidone, the structure reported was incorrect. Baillie, *et al.*[26]



19



21



22

proposed a structure (22) for vicanicin based on biogenetic arguments and analogies with known depsidones.

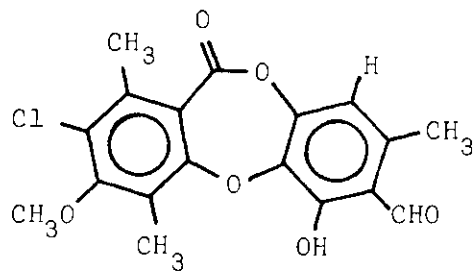
Several features of the structure proposed by Baillie were not rigorously proved and required further investigation: (1) The position of the hydroxyl group was assumed to be in the A ring; (2) the methyl group at C-1 was the only substituent assigned with certainty in the A ring; (3) the substituents at C-6 and C-7 could be interchanged.

An attempt was made to resolve these ambiguities by single crystal X-ray diffraction. Although the proposed structures for vicanicin all contained two chlorine atoms, it was desirable to introduce a heavier atom so that a classical heavy atom approach to the phase problem could be pursued. Preparation of bromoacetylvicanicin was accomplished, but crystals suitable for data collection were not obtained. Baillie had previously prepared iodoacetylvicanicin;[12] crystals of this material were twinned. Since a suitable crystalline derivative was not obtained, classical chemical degradative techniques were employed.

The hydroxyl group was shown to be in the A ring by converting vicanicin to *O*-ethylvicanicin (26) using ethereal diazoethane. The *O*-ethylvicanicin obtained (mp 185-186.5°) agreed with the reported melting point (185-186°[16]), and the nmr spectrum was satisfactory for an *O*-ethyl group (τ 8.57, t, 3H, J = 7 Hz, 6.00, q, 2H, J = 7 Hz). The spectrum also contained singlet absorptions at τ 7.70 (3H), 7.56 (3H), and 7.51 (6H) for the *C*-methyl groups and an absorption at τ 6.25 (3H) for the *O*-methyl group. The *O*-ethylvicanicin was then converted to methyl *O*-ethylvicanicate (27) by treatment with sodium and methanol. This crude material was then dissolved in acetic acid

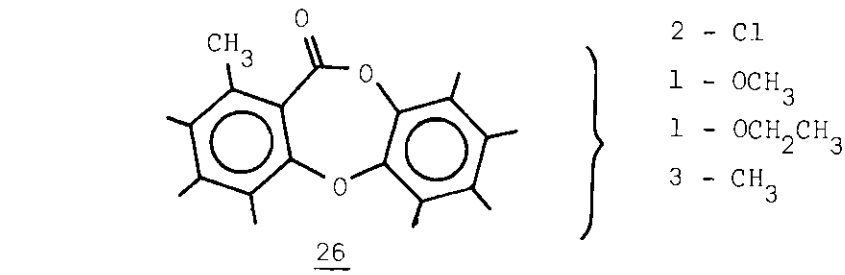
and oxidized with nitric acid according to the method of Seshadri.[16] The phenolic ester (28) that was isolated from the reaction mixture showed absorptions in the nmr spectrum consistent with an *O*-ethyl group (τ 8.55, t, 3H, *J* = 7 Hz, 5.98, q, 2H, *J* = 7 Hz). This indicated that the free hydroxyl group in vicanicin is in the A ring. This sequence of reactions is summarized in Scheme 3. The nmr spectrum of 28 also showed singlet absorptions at τ 7.80 (3H) and 7.40 (3H) for the *C*-methyl groups. The deshielded methyl group absorption at τ 7.40 indicates that this group is probably *ortho* to the carboxymethyl function.[64] Singlet absorptions at τ 6.02 (3H) and 5.98 (3H) correspond to the methoxyl group and the methyl ester group. The phenolic proton showed absorption at τ -1.30 (1H). The phenolic ester 28 was further characterized by the mass spectrum, which showed a molecular ion at *m/e* 258 (60%) (calcd for $C_{12}H_{15}{}^{35}ClO_4$: *m/e* 258) and an m+2 ion at *m/e* 260 (20%) (calcd for $C_{12}H_{15}{}^{37}ClO_4$: *m/e* 260).

The assignments of the chlorine atom at position 2, the methoxyl group at position 3, and the remaining methyl group at position 4 in 22 are tenable and were suggested by analogy to the structure of Pannarin[65] (30).



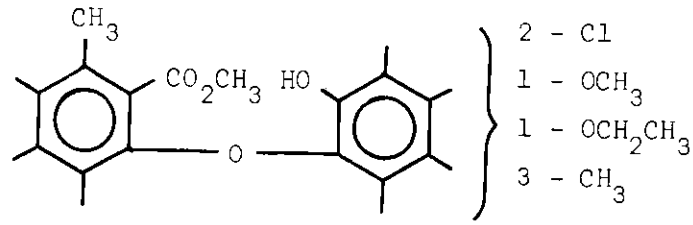
30

Scheme 3



26

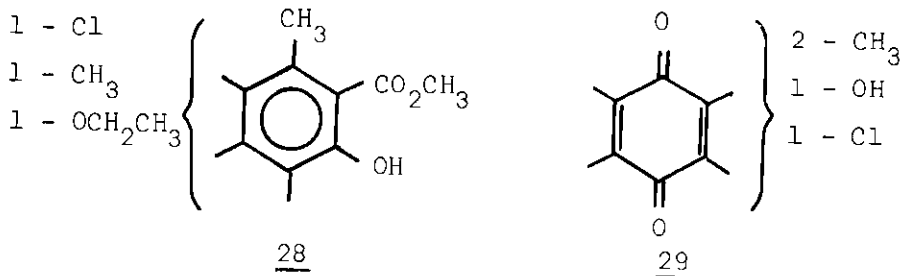
Na/CH_3OH



27

CH_3CO_2H

HNO_3



28 29

The structure proposed for the A ring by Baillie was proved by repeating the degradation sequence used by Seshadri[16] and comparing the *O*-methyl derivative of the ester formed with synthetic material. A sample of *O*-methylvicanicin (31) prepared by Balthis[23] was treated with sodium and methanol, which converted it to methyl *O*-methylvicanicate (32). The sample of 32 was oxidized with nitric acid using the method of Seshadri,[16] and the phenolic ester (33) that was isolated (mp 77-78°) from the reaction mixture agreed in melting point with that reported (77-78°[16]). The nmr spectrum of 33 showed singlet C-methyl group absorptions at τ 7.85 (3H) and 7.41 (3H). The singlet absorptions at τ 6.18 (3H) and 6.04 (3H) were assigned to the methoxyl and methyl ester groups; the phenolic hydroxyl group absorped at τ -1.40 (1H). The mass spectrum showed a molecular ion at *m/e* 244 (72%) (calcd for $C_{11}H_{13}ClO_4$: *m/e* 244). The ir spectrum showed absorptions at 3405 (intramolecularly hydrogen bonded O-H stretch), 1660 (hydrogen bonded aryl ester) and 1600, 1560, and 1445 k (aryl C-C stretch).

The sample of 33 was treated with ethereal diazomethane, and the solvent was allowed to evaporate to yield a semicrystalline material (34) mp 55-59°. The nmr spectrum of 34 showed absorptions for *C*-methyl groups at τ 7.82 (3H) and 7.78 (3H). The absorptions at τ 6.29 (3H), 6.23 (3H), and 6.14 (3H) were assigned to the two methoxyl groups and the methyl ester group. The mass spectrum showed a molecular ion at *m/e* 258 (59%) (calcd for $C_{12}H_{15}ClO_4$: *m/e* 258). The ir spectrum showed absorptions at 1735 (aryl ester) and 1590, 1560, and 1450 k

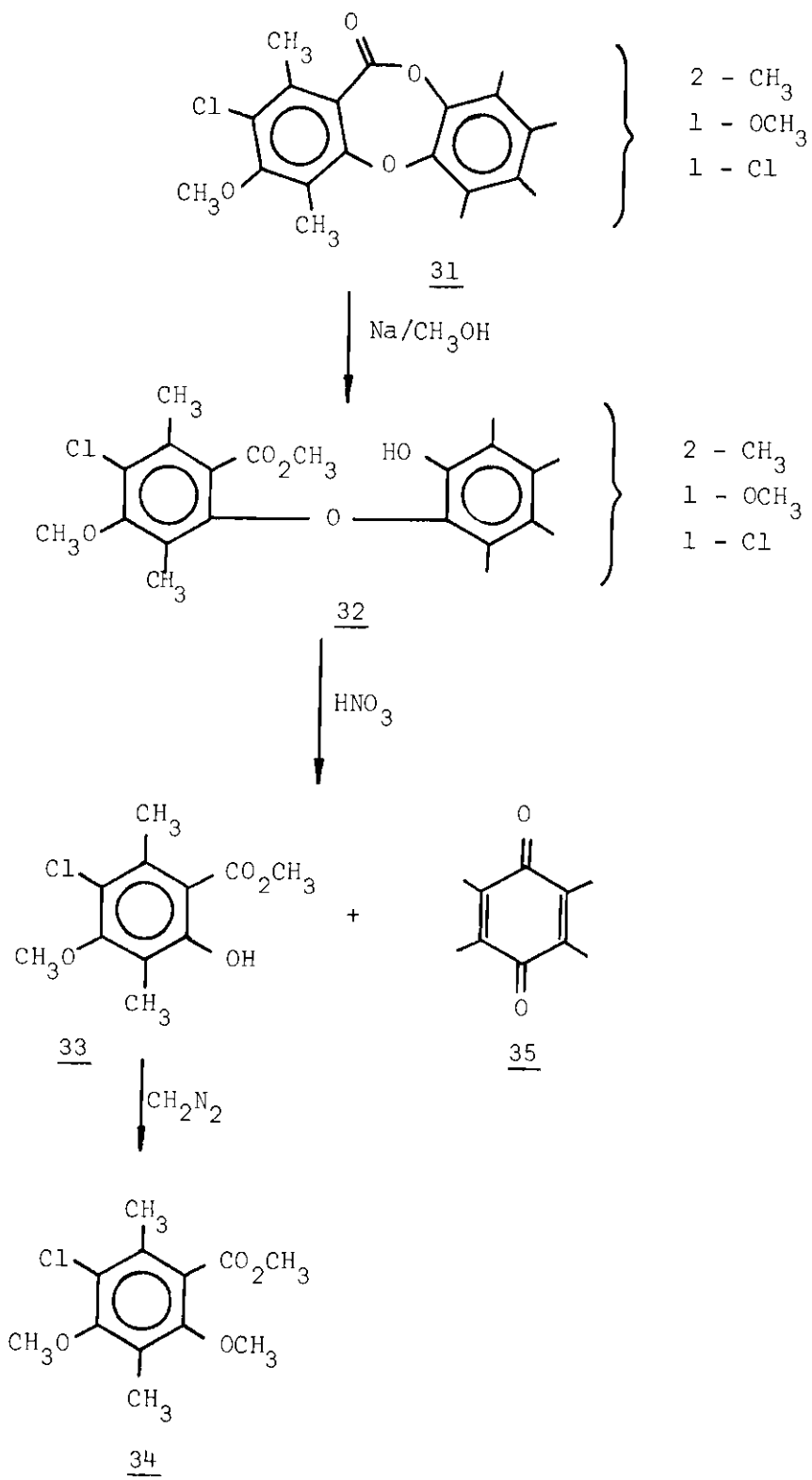
(aryl C-C stretch). This degradation sequence is summarized in Scheme 4. The sample 34 was shown to be identical with methyl 5-chloro-2,4-dimethoxy-3,6-dimethylbenzoate (36) that was synthesized by the unambiguous route shown in Scheme 5.

From commercial orcinol (37), 3,5-dimethoxytoluene (38) was prepared by methylating 37 using dimethyl sulfate. The 3,5-dimethoxytoluene was converted to 3,5-dimethoxy-*p*-xylene (39) by treating 38 with *n*-butyllithium and methylating the lithium addition compound with a dilute solution of dimethyl sulfate in ether.[66] Compound 39 was also prepared by the reduction of 2,6-dimethoxy-4-methylbenzaldehyde (40), which was prepared by treating 38 with *n*-butyllithium then *N*-methylformanilide.[67] The nmr spectrum of 39 showed *C*-methyl absorptions at τ 7.82 (3H) and 7.75 (3H). The *O*-methyl absorptions were at τ 6.42 (6H) and the aromatic protons absorped at 3.75 (2H). The mass spectrum confirmed the formula $C_{10}H_{14}O_2$ (calcd *m/e* 166: obsd *m/e* 166).

The sample of 39 was chlorinated in benzene solution using ferric chloride as the catalyst. The formula $C_{10}H_{12}Cl_2O_2$ was indicated by the exact mass of the molecular ion (calcd *m/e* 234.0213: obsd *m/e* 234.0224). The nmr spectrum contained absorptions for the *C*-methyl groups at τ 7.76 (3H) and 7.52 (3H) and the equivalent *O*-methyl groups at τ 6.22 (6H). This confirmed the structure as 2,6-dichloro-3,5-dimethoxy-*p*-xylene (41).

Compound 41 was converted to 5-chloro-2,4-dimethoxy-3,6-dimethylbenzoic acid (42) by treating it with *n*-butyllithium and reacting this mixture with dry carbon dioxide gas.[68] The mass spectrum of 42 showed a

Scheme 4


2 - CH3
1 - OCH3
1 - Cl
31
Na/CH3OH
2 - CH3
1 - OCH3
1 - Cl
32
HNO3
33
35
CH2N2
34

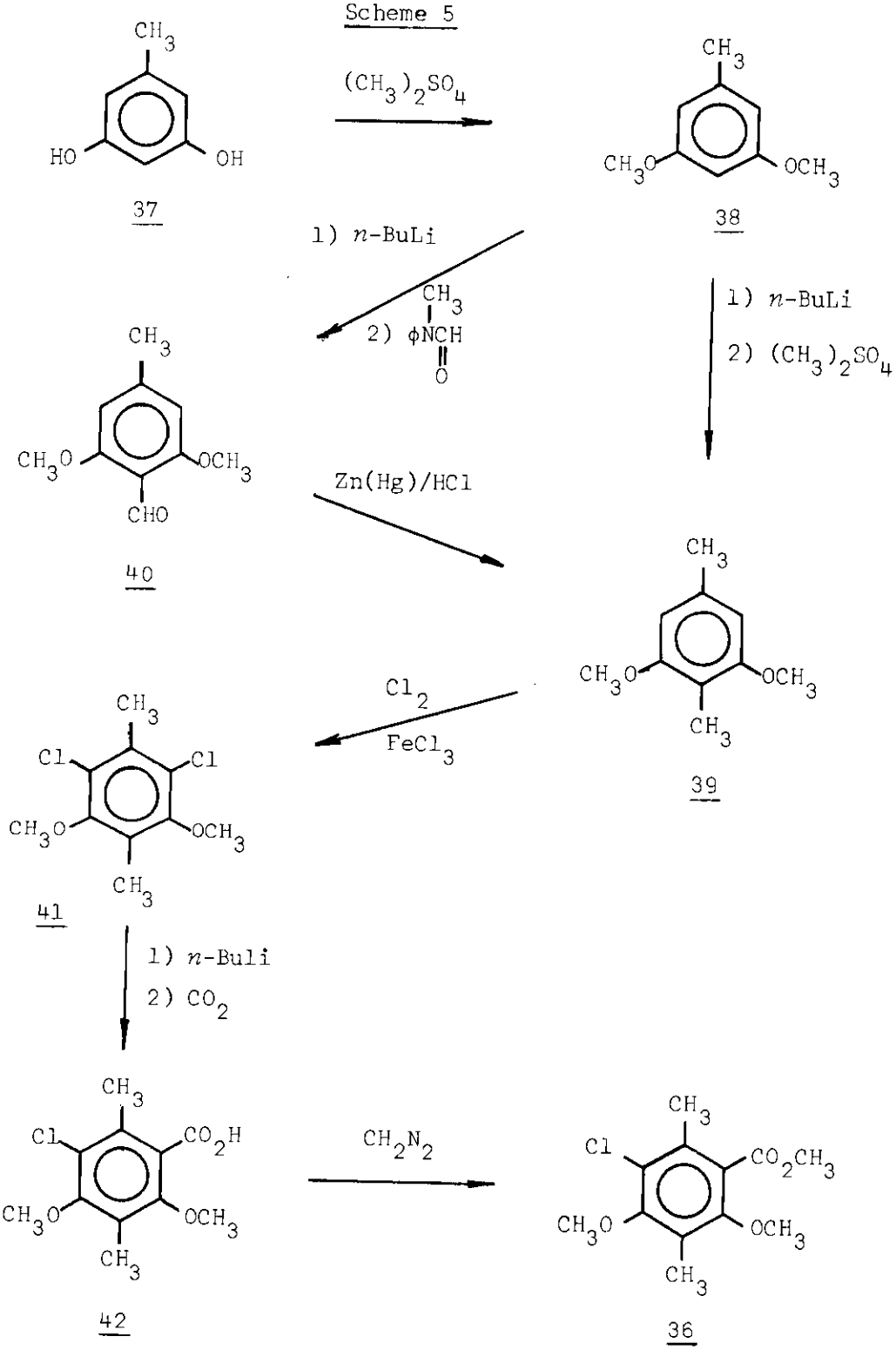
molecular ion at *m/e* 244 (100%) (calcd for $C_{11}H_{13}ClO_4$: *m/e* 244). The nmr spectrum showed singlet absorptions at τ 7.71 (3H) and 7.54 (3H) for the *C*-methyl groups, τ 6.13 (6H) for the *O*-methyl groups, and τ -0.03 (1H) for the carboxylic acid proton.

The benzoic acid 42 was converted to methyl 5-chloro-2,4-dimethoxy-3,6-dimethylbenzoate (36) by treatment with ethereal diazomethane. The nmr spectrum of 36 was identical with the nmr spectrum of 34. The mass spectrum, ir spectrum, and gas chromatogram of 36 were identical with those of 34.

Thus the A ring is identical with the A ring in structure 22 proposed by Baillie.[26] The structure of the B ring was suggested by proving the structure of the quinone (35) obtained when methyl *O*-methyl or *O*-ethylvicanicate was oxidized with nitric acid. The quinone is obtained from the reaction medium by extraction with sodium bicarbonate solution. An exact mass determination of the molecular ion (*m/e* 186.0051) indicated the formula $C_8H_7ClO_3$ (calcd *m/e* 186.0083). The structure of this quinone was shown to be 3-chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone (43)[12] by comparison with a synthetic sample.

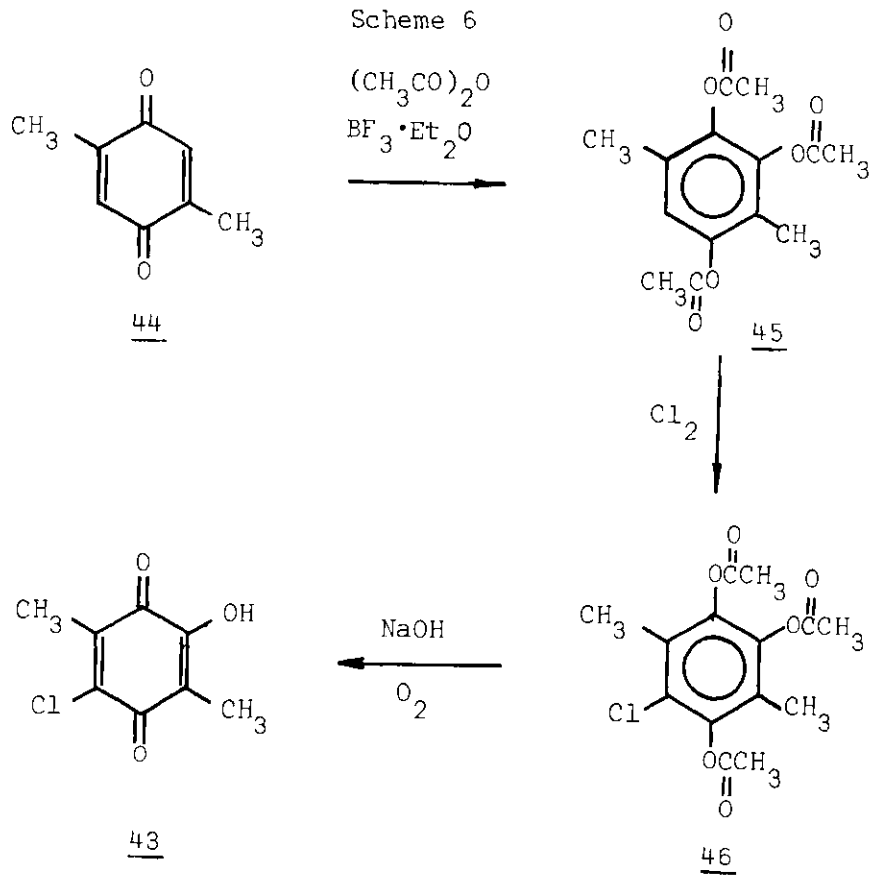
A sample of 2,5-dimethyl-*p*-benzoquinone (44) treated with acetic anhydride and boron trifluoride etherate[53] yielded 1,4,-dimethyl-2,3,5-triacetoxybenzene (45). A sample of 45 was chlorinated to yield 46. The chlorinated product was hydrolyzed using sodium hydroxide solution. The quinone 43 isolated from the hydrolysate showed an undepressed mixture melting point of 126-127° with 35. The mass spectrum and thin layer chromatograms of 43 were identical with those

Scheme 5


CH3
HO
OH
37
(CH3)2SO4
CH3
CH3O
OCH3
38
1) n-BuLi
2) φNCH
O
1) n-BuLi
2) (CH3)2SO4
CH3
CH3O
OCH3
CHO
40
Zn(Hg)/HCl
CH3
CH3O
OCH3
CH3
39
Cl2
FeCl3
CH3
Cl
Cl
CH3O
OCH3
CH3
41
1) n-Buli
2) CO2
CH3
Cl
CO2H
CH3O
OCH3
CH3
42
CH2N2
CH3
Cl
CO2CH3
CH3O
OCH3
CH3
36

of 35. The structure of the quinone 35 was thus shown to be 3-chloro-2,5-dimethyl-6-hydroxy-*p*-benzoquinone. The synthetic sequence is outlined in Scheme 6.

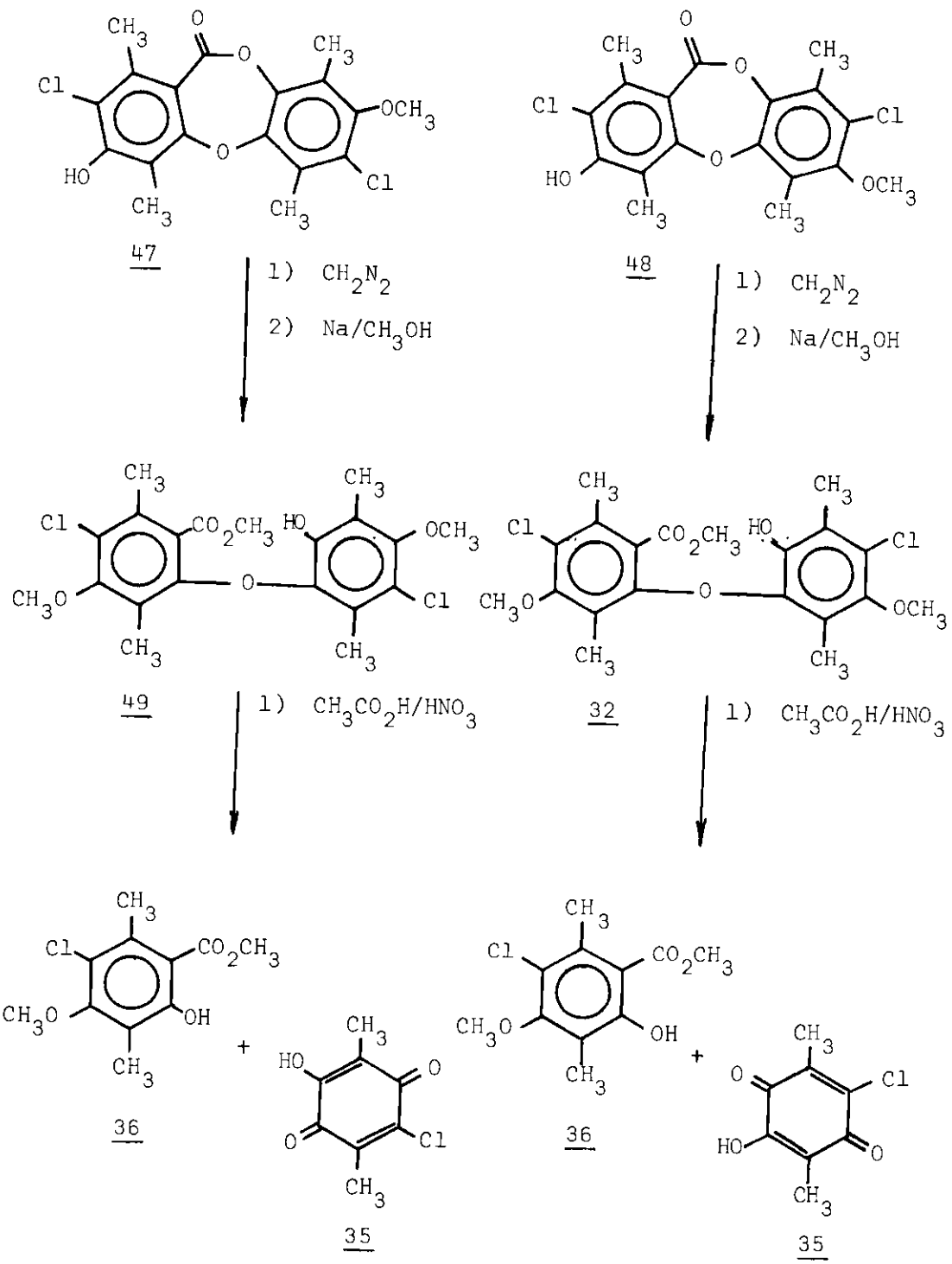
Scheme 6



44 45 46 43

The structure of the quinone 35 and the phenolic ester 36 suggests two possible structures for vicanicin, 47 and 48 as shown in Scheme 7. Structure 48 is proposed as the structure of vicanicin on the following basis. The oxidation and hydrolysis of 32 in acidic solution is believed to proceed by initial oxidation of the B ring to a *p*-benzoquinone and then hydrolysis of the phenyl ether. Structure

Scheme 7



47, however, would not allow initial oxidation and then hydrolysis since the B ring in 49 cannot be oxidized to a *p*-benzoquinone. This argument is substantiated by the fact that methyl *O,O'*-dimethylvicanicate (50), when treated under the oxidative conditions of Seshadri,[16] is recovered almost quantitatively. If the oxidation of the B ring were not the initial step, one would expect hydrolysis of the phenyl ether in 50 and isolation of the phenolic ester from the A ring (36). Therefore structure 48 is proposed as the correct structure of vicanicin.

CHAPTER IV

RECOMMENDATIONS

The compound 2-(2,3-dichloro-2-pyrrolin-1-yl)-1-pyrroline (24) was reacted with bromine in both carbon tetrachloride and chloroform solutions. The mixture of products obtained, in variable yield, should be fully characterized and the reaction conditions optimized for reproducible results. Compound 24 was also treated with a solution of iodine in carbon tetrachloride, and a product was obtained that showed a virtually identical mass spectrum with that of 24 but a different melting point. The yield of this compound was low and not reproducible. This reaction should be fully investigated. It would be interesting to subject δ valerolactam to the same conditions that 2-pyrrolidinone yielded compound 24.

If there exists some doubt as to the correct structure of vicanicin this problem could be resolved by the synthesis of *O*-methylvicanicin (31). This synthesis could begin by conversion of the methoxyl group *ortho* to the carbonyl group to a hydroxyl group in 42. This could be accomplished by the use of aluminum chloride in nitrobenzene solution, which has been shown to convert methoxyl groups *ortho* or *peri* to a carbonyl group to hydroxyl groups selectively.[69] The phenolic acid obtained could then be esterified with 3-chloro-2,5-dimethyl-4-methoxyphenol by using DCC[70] or TFAA.[71] The next step would be formation of the phenyl ether by treating the ester with

manganese dioxide in chloroform under reflux.[72] This method of oxidative coupling of phenols was used by Brown, *et al.* during the synthesis of diplocin.

The B ring phenol could be synthesized by analogy to the synthesis of compound 42 but starting with 2,5-dimethyl-*p*-benzoquinone. The 4-chloro-2,5-dimethoxy-3,6-dimethylbenzoic acid obtained could be selectively demethylated *ortho* to the carbonyl by aluminum chloride in nitrobenzene. The required phenol could be obtained by decarboxylation of the copper salt of the benzoic acid.[73] This synthesis could be modified slightly and the *O*-methyl ether of 47 could also be synthesized.

APPENDIX

DATA PROCESSING AND SCALING PROGRAM

```
C  PROGRAM TO CORRECT DIFFRACTOMETER DATA FOR BACKGROUND, CALC STANDARD
C  DEVIATIONS, AND INCLUDES OPTIONS TO SCALE DATA ACCORDING TO STANDARD
C  REFLECTIONS, PROGRAM WILL AVERAGE REFLECTIONS COLLECTED MORE THAN
C  ONCE. CONTROL CARDS ARE AS FOLLOWS**
C   FIRST CONTROL CARD* FORMAT 12I3  THIS IS THE OPTION CARD
C   SECOND   "     "  *  FORMAT 6I6  THE LOWER AND UPPER LIMITS OF THE
C                        H,K,L INDICES
C   THIRD CONTROL CARD*  FORMAT 4F10.5,I2   TST, THE TOTAL SCAN TIME,
C                        SBT, THE SINGLE BACKGR. TIME, P IGNORANCE
C                        FACTOR, SC, THE FACTOR WHICH SIGCI MUST BE LESS
C                        THAN TO BE ABOVE BACKGR.  NUMSTD, THE NUMBER OF
C                        STD. REFLECTIONS IN EACH SET
C   DATA CARDS  MASTER CARDS FROM THE DIFFRACTOMETER (1 IN COLUMN 1)
C               WILL BE IGNORED. DATA MUST HAVE ZERO OR BLANK IN COLUMN
C               1. STANDARD REFLECTIONS MUST HAVE A 5 IN COLUMN 1. DATA
C               DECK MUST BEGIN AND END WITH STD.REFLECTION CARD(S).
C              LAST CARD IN DECK MUST HAVE 9 IN COLUMN 1.
C  PROGRAM INCLUDES SUBROUTINES SYMM AND CHECK. SYMM IS FOR AVERAGING
C  SYMMETRY RELATED REFLECTIONS. CHECK ALLOWS ONE TO TRY DIFFERENT VALUES
C  OF P AND SC WITHOUT ANY OUTPUT. IF CHECK IS USED THE FOLLOWING
C  CONTROL CARDS MUST FOLLOW THE DATA DECK IF READING DATA FROM CARDS
C  OTHERWISE FOLLOWS THE THIRD CONTROL CARD.
C    FOURTH CONTROL CARD* FORMAT I3   KYCLE THE NUMBER OF SETS OF P AND
C                         SC THAT ARE TO FOLLOW
C    ALL REMAINING CONTROL CARDS* FORMAT 2F8.5 VALUES FOR P AND SC
      INTEGER C,PU,PR,CR
      REAL IW
      DIMENSION SCI(15,15,15),TIME(15,15,15),SCALE(15,15,15)
      DIMENSION AVG(200),STD(200),SG(100),COSET(100),SUM(100)
      IMPLICIT INTEGER(H,M,N)
      CR=5
      PU=1
      PR=6
      READ(CR,100) IECARD,ISYMM,ICHECK,IRTAPE,IUCARD,IPERM,J1,J2,J3,J4,I
     1ICARD,IITAPE
  100 FORMAT (12I3)
      WRITE(PR,105) IECARD,ISYMM,ICHECK,IRTAPE,IUCARD,IPERM,J1,J2,J3,J4.
     1IICARD,IITAPE
  105 FORMAT (1H1,'OPTION CARD: ',12I3)
      WRITE(PR,102) IECARD,ISYMM,ICHECK,IRTAPE,IUCARD,IPERM,IICARD,IITAP
     1E,J1,J2,J3,J4,J1,J2,J3,J4
  102 FORMAT (1HO,'IECARD = ',I3,//,' ISYMM = ',I3'//,' ICHECK = ',I3,//
     1,' IRTAPE = ',I3,//,' IUCARD = ',I3,//,' IPERM = ',I3,//,' IICARD
     2= ',I3,//,' IITAPE = ',I3,//,' PERMANENT TAPE WRITTEN ON UNIT ',I
     33,//,' SCARATCH DRUM IS UNIT ',I3,//,' SCALED OUTPUT WRITTEN ON UN
     4IT  ',I3,//,' UNSCALED OUTPUT WRITTEN ON UNIT  ',I3,//,' J1 = ',I3
```

```
   5,//,' J2 = ',I3,//,' J3 = ',I3,//,' J4 = ',I3)
    READ(CR,110) HMIN,HMAX,KMIN,KMAX,LMIN,LMAX
110 FORMAT (6I6)
    WRITE(PR,115)
115 FORMAT (1HO,'  HMIN  HMAX  KMIN  KMAX  LMIN  LMAX')
    WRITE(PR,120) HMIN,HMAX,KMIN,KMAX,LMIN,LMAX
120 FORMAT (1H ,6I6)
    MAXH=HMAX-HMIN+1
    MAXK=KMAX-KMIN+1
    MAXL=LMAX-LMIN+1
    READ(CR,125) TST,SBT,P,SC,NUMSTD
125 FORMAT (4F10.5,I2)
    WRITE(PR,130) TST,SBT,P,SC,NUMSTD
130 FORMAT (1HO,'TOTAL SCAN TIME = ',F6.2,' SEC.',//,' SINGLE BKG. TIM
   IE = ',F6.2,' SEC.',//,' IGNORANCE FACTOR (P) = ',F6.4'//,' CUTOFF
   2FACTOR (SC) = ',F6.4,//,' NUMBER OF STD.REFLECTIONS = ',I3)
    DO 200 IH=1,MAXH
    H=IH
    DO 199 IK=1,MAXK
    K=IK
    DO 198 IL=1,MAXL
    L=IL
    SCI(H,K,L)=0.0
    TIME(H,K,L)=0.0
    SCALE(H,K,L)=0.0
198 CONTINUE
199 CONTINUE
200 CONTINUE
    JOJ=0
    ICOUNT=0
    IMAT=0
    AVG(1)=0.0
    ATT1=2.7448861
    ATT2=10.90240317
    ATT3=29.66
    NUMSET=0
    IOI=1
    III=0
    WRITE(PR,290)
290 FORMAT (1H1,'  C   H   K   L   D     I       B1      B2     CORR.I
   INT.   SIGMA        SIGSQ         IW         SIGCI',//)
300 IF (IECARD.EQ.0) GO TO 460
    READ(CR,305,ERR= 306,END= 440) C,HH,KK,LL,ID,I,IB1,IB2
305 FORMAT (I1,3I3,25X,I1,3I6)
    GO TO 310
306 CONTINUE
    WRITE(PR,308)
308 FORMAT (1H ,'**********READING ERROR OR BAD CARD**************')
    GO TO 300
310 CONTINUE
```

```
      IF (C.EQ.1) GO TO 300
      IF (C.EQ.9) GO TO 440
      IF ((HH.EQ.0).AND.(KK.EQ.0).AND.(LL.EQ.0)) GO TO 300
      IF (C.EQ.5) GO TO 330
      C=0
      IMAT=IMAT+1
      ICOUNT=ICOUNT+1
  330 CONTINUE
      I=I*10
      RI=FLOAT(I)
      IB1=IB1*10
      RB1=FLOAT(IB1)
      IB2=IB2*10
      RB2=FLOAT(IB2)
      IF (ID.EQ.1) GO TO 360
      IF (ID.EQ.2) GO TO 370
      IF (ID.EQ.3) GO TO 380
      GO TO 390
  360 CONTINUE
      RI=RI*ATT1
      RB1=RB1*ATT1
      RB2=RB2*ATT1
      GO TO 390
  370 CONTINUE
      RI=RI*ATT2
      RB1=RB1*ATT2
      RB2=RB2*ATT2
      GO TO 390
  380 CONTINUE
      RI=RI*ATT3
      RB1=RB1*ATT3
      RB2=RB2*ATT3
  390 CONTINUE
      CI=((RI)-(0.5*(TST/SBT)*(RB1+RB2)))
      IF (CI) 400,400,410
  400 CONTINUE
      WRITE(PR,401) C,HH,KK,LL,ID,I,IB1,IB2
  401 FORMAT (1H ,I3,3I4,3X,I1,3X,3(I6,2X),'***CORRECT INTENSITY < ZERO*
     1**********************************')
      GO TO 300
  410 CONTINUE
      SIGSQ=((RI)+(0.25*((TST/SBT)**2)*(RB1+RB2))+(P*CI)**2)
      SIGMA=SQRT(SIGSQ)
      IW=SIGSQ/CI
      SIGCI=SIGMA/CI
      H=HH-HMIN+1
      K=KK-KMIN+1
      L=LL-LMIN+1
  440 CONTINUE
```

```
      IF (IPERM.EQ.0) GO TO 451
      WRITE(J1)    C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
  451 CONTINUE
      WRITE(J2)    C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
      GO TO 470
  460 CONTINUE
      READ(J1)                      C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,
     1RB2,SIGMA,SIGSQ,SIGCI,IW,RI
      WRITE(J2)    C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
      IF ((IECARD.EQ.0).AND.(C.NE.5)) GO TO 465
      GO TO 470
  465 CONTINUE
      ICOUNT=ICOUNT+1
      IMAT=IMAT+1
  470 CONTINUE
      WRITE(PR,475) C,HH,KK,LL,ID, I,IB1,IB2,CI,SIGMA,SIGSQ,IW,SIGCI
  475 FORMAT (1H ,I3,4I4,2X,I7,1X,2(I6,2X),5(E10.4,2X))
      IF (C.EQ.9) GO TO 580
      IF (C.EQ.5) GO TO 490
      GO TO 300
  490 CONTINUE
      JOJ=JOJ+1
      STD(JOJ)=CI
      SG(JOJ)=SIGMA
      IF (IOI,EQ.NUMSTD) GO TO 500
      IOI=IOI+1
      GO TO 300
  500 CONTINUE
      IOI=1
      COSET(NUMSET)=ICOUNT
      ICOUNT=0
      NUMSET=NUMSET+1
      GO TO 300
  580 CONTINUE
      END FILE J2
      DO 600 IN=1,NUMSET
      N=IN
      DO 598 IM=1,NUMSTD
      M=IM
      JJ=(M+(N-1)*FLOAT(NUMSTD))
      SUM(N)=SUM(N)+STD(JJ)
  598 CONTINUE
  600 CONTINUE
      WRITE(PR,602)
  602 FORMAT (1HO,'CI1+CI2+...CIN / SUM(1) ')
      XXX=SUM(1)
```

```
      DO 620 IJ=1,NUMSET
      J=IJ
      AVG(J)=XXX/SUM(J)
      WRITE(PR,604) AVG(J)
  604 FORMAT (1H ,F10.8)
  620 CONTINUE
      REWIND J2
      WRITE(PR,621)
  621 FORMAT (1HO,'   H   K   L   SCALED INTENSITY     STD.DEV.(IW)')
      DO 640 IN=1,NUMSET
      N=IN
      II=COSET(N)+1
      JJJ=II-1
      VV=FLOAT(II)
      DO 635 IJ=1,JJJ
      WW=FLOAT(IJ)
  628 CONTINUE
      READ(J2)     C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
      IF (C.EQ.9) GO TO 645
      IF (III.EQ.1) GO TO 626
      IF (C.NE.5) GO TO 626
      WRITE(PR,624) HH,KK,LL,CI,IW
  624 FORMAT (1H ,3I4,4X,F15.5,6X,F10.5)
      IF (IICARD.EQ.0) TO GO 6000
      WRITE(PU,625) HH,KK,LL,CI,IW
  625 FORMAT (3I5,F15.5,F10.5)
 6000 CONTINUE
      IF (IITAPE.EQ.1) GO TO 6100
      WRITE(J3)      C,HH,KK,LL,CI,IW
 6100 CONTINUE
      GO TO 628
  626 CONTINUE
      IF (C.EQ.5) GO TO 628
      III=1
      SCALE(H,K,L)=(AVG(N)+((AVG(N+1)-AVG(N))*WW/VV))
      SCI(H,K,L)=(SCI(H,K,L)+SCALE(H,K,L)*CI)/TIME(H,K,L)+1.0
      TIME(H,K,L)=TIME(H,K,L)+1.0
  635 CONTINUE
  640 CONTINUE
  645 CONTINUE
      IF (ISYMM.EQ.0) GO TO 650
      CALL SYMM (KOW,IUCARD,IRCARD,IRTAPE,IMAT,MAXH,MAXK,MAXL,SCI,HMIN,
     1KMIN,LMIN,SC,J2,J3,PR,PU)
      CONTINUE
      GO TO 725
  650 CONTINUE
      WRITE(PR,651)
  651 FORMAT (1HO,' C   H   K   L   SCALED INTENSITY  STD.DEV.(IW)   TIM
     1E    SCALE(H,K,L)')
```

```
      REWIND J2
  655 CONTINUE
      READ(J2)     C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
      IF (C.EQ.9) GO TO 705
      IF (C.EQ.5) GO TO 655
      IF (LL.GT.0) GO TO 655
      KNOW=KNOW+1
      IF (SIGCI-SC) 665,655,655
  665 CONTINUE
      KOW=KOW+1
      IF (IUCARD.EQ.0) GO TO 685
      WRITE(PU,680) HH,KK,LL,SCI(H,K,L),IW
  680 FORMAT (3I5,F15.5,F10.5)
  685 CONTINUE
      IF (IRTAPE.EQ.1) GO TO 695
      WRITE(J3)     HH,KK,LL,SCI(H,K,L),IW
  695 CONTINUE
      WRITE(PR,700) C,HH,KK,LL,SCI(H,K,L),IW,TIME(H,K,L),SCALE(H,K,L)
  700 FORMAT (1H ,I2,3I4,4X,F15.5,4X,F10.5,3X,F4.1,6X,F10.8)
      GO TO 655
  705 CONTINUE
      WRITE(PR,710) IMAT,KNOW,KOW
  710 FORMAT (1HO,'TOTAL NUMBER COLLECTED = ',I5,//,' REFLECTIONS WITH S
     1CI > ZERO = ',I5,//,' REFLECTIONS WITH SIGCI < SC = ',I5)
  725 CONTINUE
      IF (ICHECK.EQ.1) GO TO 730
      CALL CHECK (TST,SBT,CR,PR,J2)
  730 CONTINUE
      END
```

```
      SUBROUTINE CHECK (TST,SBT,CR,PR,J2)
      REAL IW
      INTEGER C,PR,CR
      JJ=0
      READ(CR,1000) KYCLE
 1000 FORMAT (I3)
      WRITE(PR,1005) KYCLE
 1005 FORMAT (1H1,'NUMBER OF CYCLES = ',I3)
 1010 CONTINUE
      REWIND J2
      READ(CR,1015) P,SC
 1015 FORMAT (2F8.5)
      WRITE(PR,1020) P,SC
 1020 FORMAT (1H ,'P= ',F8.6,/,' SC= ',F8,6)
 1030 CONTINUE
      READ(J2)     C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
       IF (C.EQ.9) GO TO 1050
       IF (C.EQ.5) GO TO 1030
       KUMBER=KUMBER+1
       SIGSQ=((RI)+(0.25*((TST/SBT)**2)*(RB1+RB2))+(P*RI)**2)
       SIGMA=SQRT(SIGSQ)
       SIGCI=SIGMA?CI
       IF (SIGCI-SC) 1040,1030,1030
 1040 CONTINUE
      KOKAL=KOKAL+1
      GO TO 1030
 1050 CONTINUE
      WRITE(PR,1065) KUMBER,KOKAL
 1065 FORMAT (1H ,'TOTAL NUMBER OF REFLECTIONS = ',I5,/,' NUMBER OF REFL
     1ECTIONS WITH SIGCI < SC = ',I5)
      KOKAL=0
      KUMBER=0
      JJ=JJ+1
      IF (JJ.EQ.KYCLE) GO TO 1070
      GO TO 1010
 1070 CONTINUE
      RETURN
      END
```

```
      SUBROUTINE SYMM (KOW,IUCARD,IRCARD,IRTAPE,IMAT,MAXH,MAXK,MAXL,SCI,
     1HMIN,KMIN,LMIN,SC,J2,J3,PR,PU)
      REAL IW
      INTEGER C,PU,PR
      DIMENSION Q(13,13,13),S(13,13,13),V(13,13,13),SCI(13,13,13)
      IMPLICIT INTEGER(H,M,N)
      DO 1800 IH=1,MAXH
      H=IH
      DO 1750 IK=1,MAXK
      K=IK
      DO 1700 IL=1,MAXL
      L=IL
      Q(H,K,L)=0.0
      S(H,K,L)=0.0
      V(H,K,L)=0.0
1700  CONTINUE
1750  CONTINUE
1800  CONTINUE
      REWIND J2
2000  CONTINUE
      READ(J2)     C,HH,KK,LL,H,K,L,ID,CI,I,IB1,RB1,IB2,RB2,SIGMA,SIGSQ,
     1SIGCI,IW,RI
      IF (C.EQ.9) GO TO 2090
      IF (C.EQ.5) GO TO 2000
      IF (LL.LT.0) GO TO 2020
      GO TO 2030
2020  CONTINUE
      HH=-HH
      LL=-LL
      HI=HH-HMIN+1
      LI=LL-LMIN+1
      GO TO 2050
2030  CONTINUE
      IF ((LL.EQ.0).AND.(HH.LT.0)) GO TO 2040
      GO TO 2080
2040  CONTINUE
      HH=-HH
      HI=HH-HMIN+1
      LI=LL
2050  CONTINUE
      Q(HI,K,LI)=(Q(HI,K,LT)+SCI(H,K,L))/V(HT,K,LI)+1.0
      S(HI,K,LI)=(S(HI,K,LI)+SIGMA)/V(HI,K,LI)+1.0
      V(HI,K,LI)=V(HI,K,LI)+1.0
      GO TO 2000
2080  CONTINUE
      Q(H,K,L)=(Q(H,K,L)+SCI(H,K,L))/V(H,K,L)+1.0
      S(H,K,L)=(S(H,K,L)+SIGMA)/V(H,K,L)+1.0
      V(H,K,L)=V(H,K,L)+1.0
      GO TO 2000
2090  CONTINUE
```

```
      WRITE(PR,2095)
2095 FORMAT (1H1,'   H   K   L  SCALED INTENSITY  STD.DEVIATION (IW)
     1TIMES COLLECTED')
      DO 3050 IH=1,MAXH
      H=IH
      DO 3048 IK=1,MAXK
      K=IK
      DO 3046 IL=1,MAXL
      L=IL
      IF (Q(H,K,L)-0.01) 3046,3046,2097
2097 CONTINUE
      SIGMA=S(H,K,L)
      SCO=Q(H,K,L)
      SIGSQ=SIGMA*SIGMA
      IW=SIGSQ/SCO
      SIGCI=SIGMA/SCO
      IOW=IOW+1
      IF (SIGCI-SC) 3000,3035,3035
3000 CONTINUE
      KTR=KTR+1
      HH=H+HMIN-1
      KK=K+KMIN-1
      LL=L+LMIN-1
      WRITE(PR,3010) HH,KK,LL,SCO,IW,V(H,K,L)
3010 FORMAT (1H ,3I4,3X,F15.5,3X,F15.5'10X,F5.1)
      IF (IUCARD.EQ.0) GO TO 3025
      WRITE(PU,3020) HH,KK,LL,SCO,IW
3020 FORMAT (3I5,F15.5,F10.5)
3025 CONTINUE
      IF (IRTAPE.EQ.1) GO TO 3035
      WRITE(J3)      HH,KK,LL,SCO,IW
3035 CONTINUE
3046 CONTINUE
3048 CONTINUE
3050 CONTINUE
      WRITE(PR,3060) IMAT
3060 FORMAT (1H ,'TOTAL NUMBER OF REFLECTIONS COLLECTED ' ',I5)
      WRITE(PR,3070) KOW
3070 FORMAT (1H ,'NUMBER OF REFLECTIONS WITH SCI > ZERO = ',I5)
      WRITE(PR,3080) IOW
3080 FORMAT (1H ,'NUMBER OF UNIQUE REFLECTIONS = ',I5)
      WRITE(PR,3090) KTR
3090 FORMAT (1H ,'NUMBER OF UNIQUE REFLECTIONS WITH SIGCI < SC = ',I5)
      CONTINUE
      RETURN
      END
```

LITERATURE CITED*

1. A. C. Finlay, G. L. Hobby, F. Hochstein, T. M. Lees, T. F. Lenert, J. A. Means, S. Y. P'An, P. P. Regna, J. B. Routien, B. A. Sobin, K. B. Tate, and J. H. Kane, *Amer. Rev. Tuberc., 63,* 1 (1951).

2. Q. R. Bartz, J. Ehrlich, J. D. Mold, M. A. Penner, and R. M. Smith, *Ibid., 63,* 4 (1951).

3. C. A. Werner, R. Tompsett, C. Muschenheim, and W. McDermott, *Ibid., 63,* 49 (1951).

4. T. H. Haskell, S. A. Fusari, R. P. Frohardt, and Q. R. Bartz, *J. Amer. Chem. Soc., 74,* 599 (1952).

5. J. R. Dyer, C. K. Kellogg, R. F. Nassar, and W. E. Streetman, *Tetrahedron Lett.,* 585 (1965).

6. W. E. Streetman, Ph.D. Thesis, Georgia Institute of Technology, Atlanta, Georgia, 1968.

7. J. C. Floyd, Ph.D. Thesis, Georgia Institute of Technology, Atlanta, Georgia, 1968.

8. J. H. Bowie, A. W. Johnson, and G. Thomas, *Tetrahedron Lett.,* 863 (1964).

9. J. C. Floyd, J. A. Bertrand, and J. R. Dyer, *Chem. Commun.* 998 (1968).

10. B. W. Bycroft, D. Cameron, L. R. Croft, A. W. Johnson, T. Webb, and P. Coggan, *Tetrahedron Lett.,* 2925 (1968).

11. J. Tafel and O. Wassmuth, *Chem. Ber., 40,* 2831 (1907).

12. A. C. Baillie, Georgia Institute of Technology, private communication, 1967.

13. W. Zopf, *Justus Liebigs Ann. Chem., 340,* 300 (1905).

14. T. R. Seshadri and S. S. Subramanian, *Proc. Indian Acad. Sci. Sect. A, 30,* 67 (1959).

---

*For the complete titles of all journals referred to, see *ACCESS*, 1969.

15. T. R. Rajagopalan and T. R. Seshadri, *Ibid., 49,* 1 (1959).

16. S. Neelakantan, T. R. Seshadri, and S. S. Subramanian, *Tetrahedron, 18,* 597 (1962).

17. P. A. Spillane, J. Keane, and T. J. Nolan, *Sci. Proc. Roy. Dublin Soc., 21,* 333 (1936).

18. F. M. Dean, J. C. Roberts, and A. Robertson, *J. Chem. Soc.,* 1432 (1954).

19. T. J. Nolan and D. Murphy, *Sci. Proc. Roy. Dublin Soc., 22,* 315 (1940).

20. L. F. Fieser and M. I. Ardo, *J. Amer. Chem. Soc., 78,* 776 (1956).

21. K. C. Rice, R. A. Heckman, and V. M. Balthis, unpublished work in these laboratories.

22. C. W. Dodge, University of Vermont, private communication, 1965.

23. V. M. Balthis, M. S. Thesis, Georgia Institute of Technology, Atlanta, Georgia, 1967.

24. J. C. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960, p 298.

25. A. C. Baillie, Georgia Institute of Technology, unpublished work in these laboratories, 1968.

26. A. C. Baillie, V. M. Balthis, and J. R. Dyer, Abstracts, Nineteenth Annual Southeastern Regional Meeting American Chemical Society, p 61.

27. *University of Texas Publication No. 5109,* University of Texas, Austin, Texas (1951).

28. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N. Y., 1968, p 1109.

29. *Ibid.,* p 191.

30. J. A. Moore and D. E. Reed, *Org. Syn., 41,* 16 (1961).

31. M. J. Buerger, "The Precession Method," John Wiley and Sons, Inc., New York, N. Y., 1964.

32. *Ibid.,* p 82.

33. N. F. M. Henery and K. Lonsdale, Eds., "International Tables for X-Ray Crystallography," Vol. I, Kynoch Press, New York, N. Y., 1962, p 106.

34. A. Zalkin, Fortran Fourier Analysis Program, FORDAP.

35. M. J. Buerger, "Crystal-Structure Analysis," John Wiley and Sons, Inc., New York, N. Y., 1960, p 206.

36. N. F. M. Henery and K. Lonsdale, Eds., "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, New York, N. Y., 1962, pp 163-216.

37. *Ibid.*, Vol. III, p 157-200.

38. M. J. Buerger, "Crystal-Structure Analysis," John Wiley and Sons, Inc., New York, N. Y., 1960, p 509.

39. G. H. Stout and L. H. Jensen, "X-Ray Structure Determination," The Macmillan Co., New York, N. Y., 1968, pp 270-288.

40. *Ibid.*, p 245.

41. W. R. Busing, K. O. Martin, and H. A. Levy, Fortran Crystallographic Least-Squares Program, XFLS (Modified Version of ORFLS), Oak Ridge National Laboratories.

42. N. F. M. Henery and K. Lonsdale, Eds., "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, New York, N. Y., 1962, pp 213-216.

43. W. C. Hamilton, *Acta Crystallog., 18,* 502 (1965).

44. A. Cooper and D. A. Norton, *A. C. Crystallog. Sect. B, 24,* 811 (1968).

45. F. H. Allen, S. Neidle and D. Rogers, *Chem. Commun.,* 308 (1968).

46. "Full Circle Goniostat Alignment," Picker Instruments, Cleveland, Ohio (1968).

47. F. Carter, "Master Card Program for the Picker Four-Angle Programmer," Picker Instruments, Cleveland, Ohio (1967).

48. C. E. Kirkwood, Georgia Institute of Technology, private communication, 1969.

49. J. A. Bertrand and C. E. Kirkwood, *Inorg. Chim. Acta., 3,* No. 4 (1969).

50. P. W. R. Cornfield, R. J. Doedens, and J. A. Ibers, *Inorg. Chem.*, *6*, 197 (1967).

51. I. M. Heilbron, Ed., "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p 263.

52. R. Adams, H. Wolff, C. K. Cain, and J. H. Clark, *J. Amer. Chem. Soc.*, *62*, 1770 (1940).

53. L. F. Fieser and M. I. Ardao, *J. Amer. Chem. Soc.*, *78*, 779 (1956).

54. C. K. Johnson, "ORTEP: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," Oak Ridge National Laboratory, 1965.

55. Y. L. Oh and E. N. Maslen, *Acta Crystallog. Sect. B*, *24*, 883 (1968).

56. J. A. Kelley, Ph.D. Thesis, Georgia Institute of Technology, Atlanta, Georgia, 1970.

57. T. Kitagawa, Y. Sawada, T. Miura, T. Ozasa, and H. Taniyama, *Tetrahedron Lett.*, 109 (1968).

58. I thank Professor E. M. Burgess for assistance in formulating this mechanism, Georgia Institute of Technology, 1970.

59. I thank Dr. K. L. Loening for providing correct names for theses compounds; also see *J. Amer. Chem. Soc.*, *90*, 509 (1968).

60. L. Ghosez, B. Haveaux, and H. G. Viehe, *Angew. Chem. Int. Ed. Engl.*, *8*, 454 (1969).

61. R. Buyle and H. G. Viehe, *Tetrahedron*, *24*, 4217 (1968).

62. V. Wolf and W. Block, *Justus Liebigs Ann. Chem.*, *637*, 119 (1960).

63. A. J. Speziale and R. C. Freeman, *J. Amer. Chem. Soc.*, *82*, 903 (1960).

64. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 79.

65. E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. IIIB, Elsevier Publishing Co., New York, N. Y., 1956, p 804.

66. R. A. Barnes and W. M. Bush, *J. Amer. Chem. Soc.*, *81*, 4705 (1959).

67. R. Adams and J. Mathieu, *J. Amer. Chem. Soc., 70,* 2120 (1948).

68. F. M. Walker, Georgia Institute of Technology, private communication, 1969.

69. E. Hardegger, E. Widmer, K. Steiner, and A. Pfiffner, *Helv. Chim. Acta, 47,* 2027 (1964).

70. S. Neelakantan, R. Padmasani, and T. R. Seshadri, *Tetrahedron, 21,* 3531 (1965).

71. R. C. Parish and L. M. Stock, *J. Org. Chem., 26,* 177 (1961).

72. C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.,* 393, 1960.

73. E. Piers and R. K. Brown, *Can. J. Chem., 40,* 559 (1962).

VITA

Fred L. Suddath, Jr. was born May 6, 1942 in Macon, Georgia. He attended elementary schools there until he moved to Rome, Georgia, in October, 1953. He attended elementary and secondary schools in Rome and was graduated from West Rome High School in May, 1960. He attended Darlington School for Boys in Rome where he was graduated in June, 1961. In September of 1961 he entered the Georgia Institute of Technology and in June, 1965 was graduated with a Bachelor of Science degree in Chemistry. In September, 1965 he began graduate study at the Georgia Institute of Technology.

On September 4, 1965 he married the former Frances Lee Gafford and is the father of a son, Brantley Vincent Suddath.

He has been awarded a National Institutes of Health Postdoctoral Fellowship for study with Professor Alexander Rich at the Massachusetts Institute of Technology in the field of X-ray crystallography.