

1966

The chemistry of 6-hydroxycrinamine and related compounds

Charles Franklin Murphy
Iowa State University

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THE CHEMISTRY OF 6-HYDROXYCRINAMINE AND
RELATED COMPOUNDS.

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THE CHEMISTRY OF 6-HYDROXYCRINAMINE
AND RELATED COMPOUNDS

BY

CHARLES FRANKLIN MURPHY

A DISSERTATION SUBMITTED TO THE
GRADUATE FACULTY IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
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MAJOR SUBJECT: ORGANIC CHEMISTRY

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Signature was redacted for privacy.

IN CHARGE OF MAJOR WORK

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DEAN OF GRADUATE COLLEGE

IOWA STATE UNIVERSITY
OF SCIENCE AND TECHNOLOGY
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1966

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INTRODUCTION

OF THE MANY ALKALOIDS DERIVED FROM THE AMARYLLIDACEAE PLANT FAMILY 6-HYDROXYCRINAMINE, HAEMANTHIDINE, CRIWELLINE AND TAZETTINE ARE PARTICULARLY INTERESTING. THIS INTEREST ARISES NOT ONLY FROM THEIR UNUSUAL STRUCTURES BUT ALSO FROM THE NOVEL REACTIONS AND REARRANGEMENTS THEY UNDERGO.

6-HYDROXYCRINAMINE AND HAEMANTHIDINE ARE UNIQUE AMONG THE ALKALOIDS POSSESSING THE 5,10_B-ETHANOPHENANTHRIDINE NUCLEUS BECAUSE THESE TWO ALKALOIDS ALONE HAVE A HYDROXYL GROUP AT C-6.^{1, p. 369} CRIWELLINE AND TAZETTINE ARE THE ONLY TWO ALKALOIDS KNOWN TO CONTAIN THE [2]BENZOPYRANO[3,4_C]INDOLE RING SYSTEM.^{1, p. 343} 6-HYDROXYCRINAMINE IS THE C-3 EPIMER OF HAEMANTHIDINE AND A SIMILAR RELATIONSHIP EXISTS BETWEEN CRIWELLINE AND TAZETTINE. THE TWO RING SYSTEMS ARE INTERRELATED BY THE REARRANGEMENTS OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE TO CRIWELLINE AND TAZETTINE, RESPECTIVELY. THE STRUCTURES OF THESE ALKALOIDS HAVE BEEN WELL ESTABLISHED BY CLASSICAL CHEMICAL TECHNIQUES SUPPLEMENTED BY INFRARED AND ULTRAVIOLET SPECTROSCOPY.

THE MECHANISMS OF THE RING SYSTEM INTERCONVERSIONS ARE UNKNOWN. A MECHANISM INVOLVING A HYDRIDE SHIFT HAS BEEN PROPOSED,^{2, p. 941} HOWEVER NO EVIDENCE HAS BEEN PRESENTED IN ITS BEHALF. THE ALKALOID INTERCONVERSION MECHANISM MERITS STUDY NOT ONLY FOR THE KNOWN IN VITRO CONVERSIONS BUT ALSO FOR THE POSSIBLE IN VIVO TRANSFORMATIONS.

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY (N.M.R.)³ AND

MASS SPECTROMETRY⁴ HAVE BEEN SHOWN TO BE USEFUL METHODS FOR STRUCTURE ELUCIDATION PROBLEMS, HOWEVER THEIR APPLICATION TO THE AMARYLLIDACEAE ALKALOIDS HAS BEEN LIMITED.^{5,6} STUDIES UTILIZING THESE METHODS COULD PROVIDE CORROBORATING EVIDENCE FOR THE PROPOSED ALKALOID STRUCTURES AS WELL AS A BASIS FOR STUDYING ALKALOIDS WITH UNKNOWN STRUCTURES.

MACRONINE, AN ALKALOID OF UNKNOWN STRUCTURE, WAS RECENTLY ISOLATED FROM CRINUM MACRANTHERUM ENGL.⁷ CRIWELLINE AND CRINAMINE WERE ISOLATED FROM THE SAME PLANT, WHICH SUGGESTS THAT MACRONINE MIGHT BE STRUCTURALLY RELATED. A WORKING KNOWLEDGE OF THE N.M.R. SPECTRA OF THE VARIOUS ALKALOIDS OF KNOWN STRUCTURES WILL PROVIDE A BASIS FOR THE STRUCTURAL STUDIES OF MACRONINE.

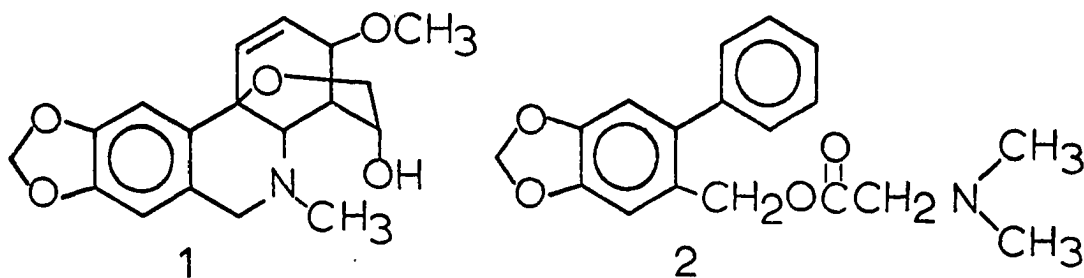
THE WORK DESCRIBED IN THIS THESIS IS A STUDY OF THE STRUCTURAL RELATIONSHIPS OF THE AFOREMENTIONED ALKALOIDS. IT IS SHOWN THAT THE 6-HYDROXYCRINAMINE-CRIWELLINE REARRANGEMENT MAY BE ONLY PARTLY EXPLAINED BY A HYDRIDE SHIFT MECHANISM. STRUCTURES ARE PROPOSED FOR MACRONINE AND INTERMEDIATES IN ITS PREPARATION FROM 6-HYDROXYCRINAMINE. NUCLEAR MAGNETIC RESONANCE STUDIES SHOW THAT 6-HYDROXYCRINAMINE AND HAEMANTHIDINE HAVE AN UNUSUAL STRUCTURAL FEATURE. MASS SPECTROMETRIC STUDIES HAVE PROVIDED A FOUNDATION ON WHICH FURTHER STRUCTURAL STUDIES MAY BE BASED. CHEMICAL STUDIES HAVE PROVIDED AN INSIGHT INTO THE REACTIVITY OF THESE ALKALOIDS, HOWEVER SOME QUESTIONS REMAIN UNANSWERED.

HISTORICAL

THE STRUCTURES AND STEREOCHEMISTRY ASSIGNED TO 6-HYDROXY-CRINAMINE, HAEMANTHIDINE, CRIWELLINE AND ALL OF THE ALKALOIDS DERIVED FROM 5,10B-ETHANOPHENANTHRIDINE ARE BASED UPON THE STRUCTURE OF TAZETTINE. A DISCUSSION OF THE STRUCTURE AND STEREOCHEMISTRY OF TAZETTINE WILL PROVIDE A FOUNDATION FOR THE STUDIES OF THE REMAINING ALKALOIDS.

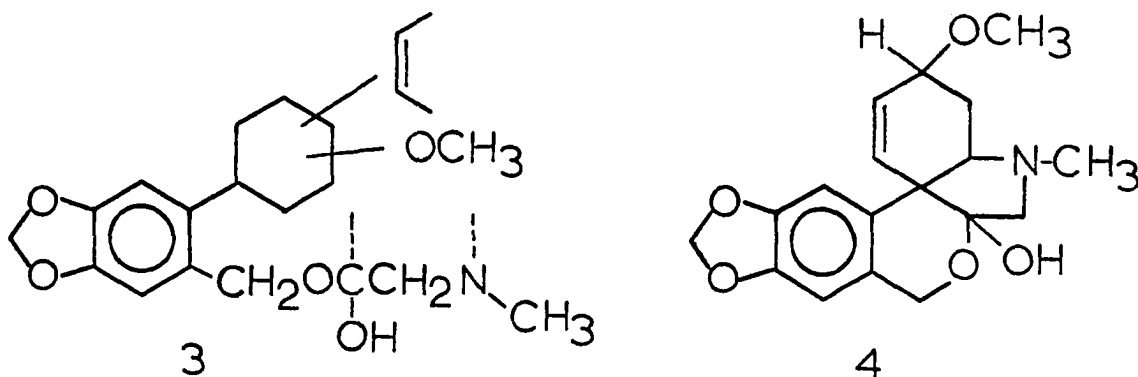
TAZETTINE

WENKERT SUMMARIZED AND ANALYZED MUCH OF THE WORK AIMED AT THE ELUCIDATION OF THE TAZETTINE STRUCTURE AND SUGGESTED THAT IN LIGHT OF THE AVAILABLE EVIDENCE, STRUCTURE 1 REPRESENTED TAZETTINE.⁸ HOWEVER THIS STRUCTURE FAILED TO PREDICT THE STRUCTURE OF THE HOFMANN METHINE WHICH WAS SHOWN TO BE N,N-DIMETHYL-6-PHENYLPIPERONYL GLYCINATE (2).⁹ IKEDA ET AL.¹⁰ SUGGESTED THAT SINCE THERE IS NO CARBONYL GROUP IN TAZETTINE BUT

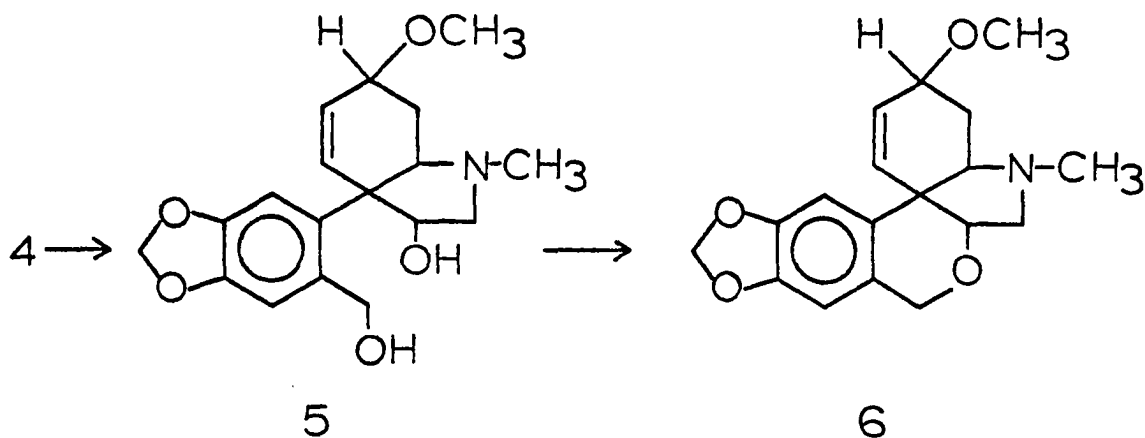


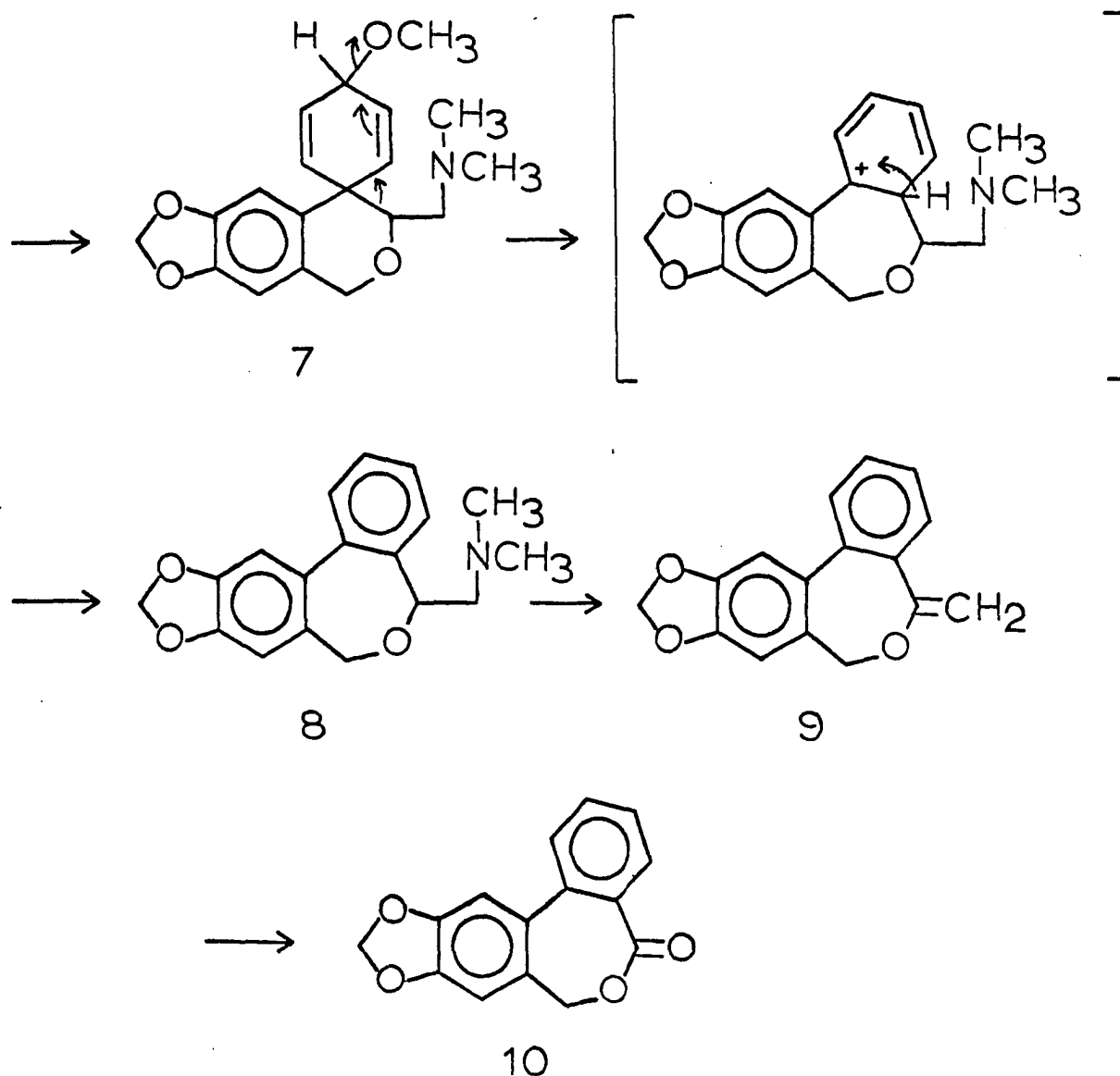
AN ESTER GROUP IS PRESENT IN THE METHINE, TAZETTINE MUST CONTAIN A MASKED CARBONYL GROUP. IT WAS PROPOSED THAT THE ESTER OF N,N-DIMETHYL GLYCINE ORIGINATED WITH THE PARTIAL STRUCTURE 3 (THE DOTTED LINES INDICATE BONDS BROKEN DURING THE HOFMANN

DEGRADATION). WITH THE STRUCTURE OF THE METHINE AS THE KEY, STRUCTURE 4 WAS SUGGESTED FOR TAZETTINE.¹⁰ THE PRESENCE OF THE HEMIKETAL GROUPING WAS CONFIRMED BY REDUCING TAZETTINE WITH LITHIUM ALUMINUM HYDRIDE TO TAZETTADIOL (5). TAZETTADIOL

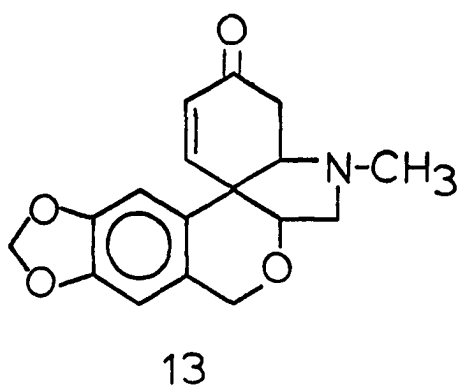
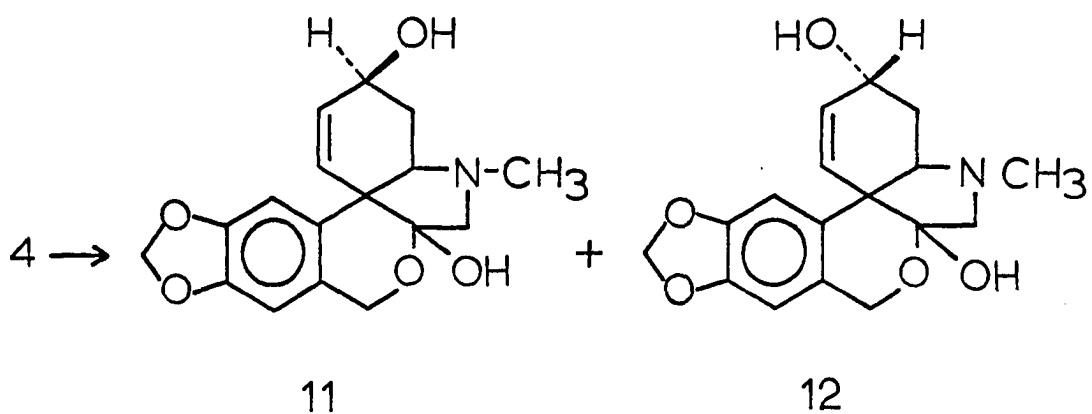


WAS CYCLIZED TO DEOXYTAZETTINE (6) WITH ACID. A HOFMANN DEGRADATION OF DEOXYTAZETTINE LED TO THE METHINE 7 WHICH IN THE PRESENCE OF ACID ELIMINATES METHANOL TO GIVE THE NEOMETHINE 8. THE NEOMETHINE WAS SUBJECTED TO A HOFMANN DEGRADATION AND TRIMETHYLAMINE AND THE NON-NITROGENOUS COMPOUND 9 WERE OBTAINED AS PRODUCTS. PERMANGANATE OXIDATION OF THE EXO METHYLENE CONVERTS THE OLEFIN 9 TO THE LACTONE 10. THE STRUCTURE OF THE LACTONE WAS PROVEN BY SYNTHESIS.

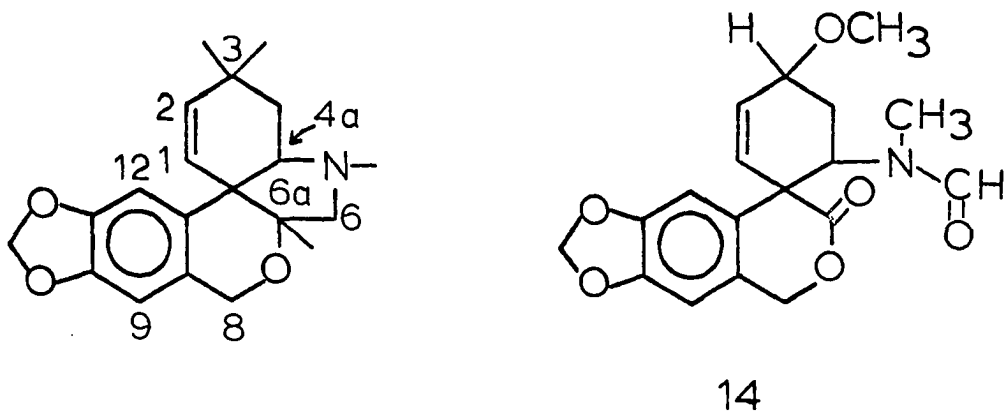




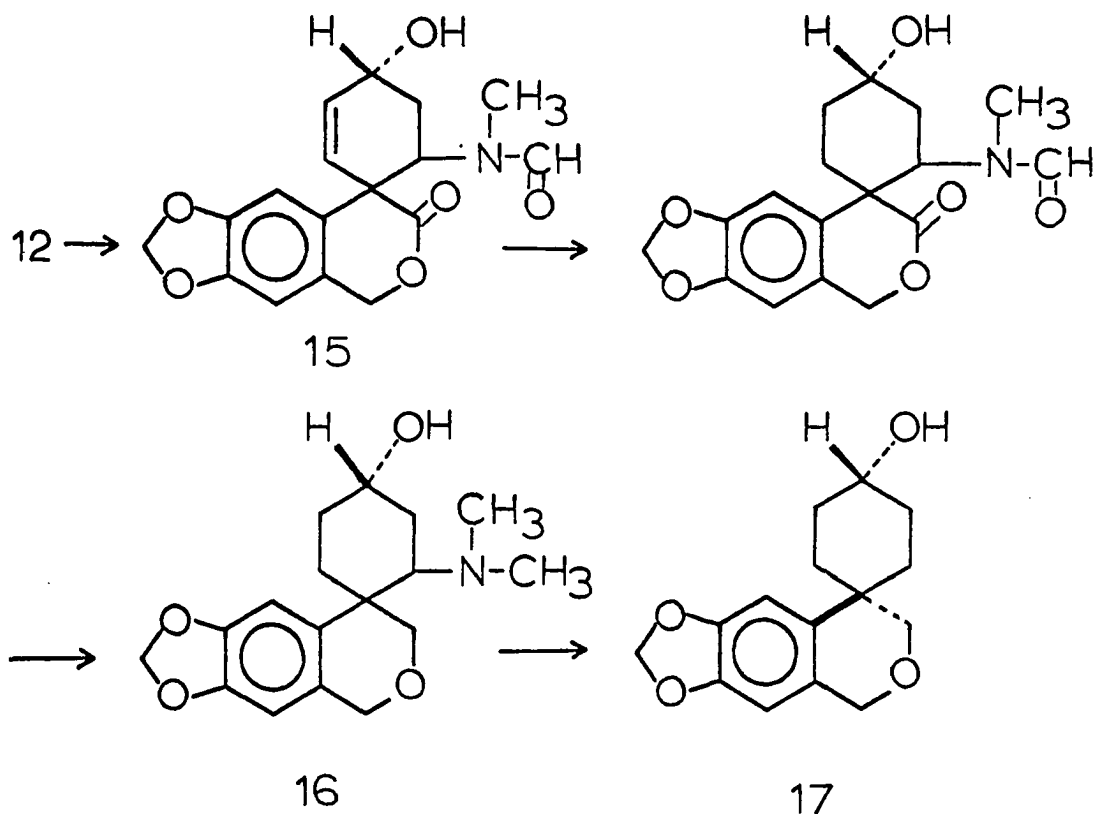
ACID HYDROLYSIS OF TAZETTINE YIELDS TWO ALCOHOLS, TAZETTINOL (11) AND ISOTAZETTINOL (12).¹⁰ METHYLATION OF TAZETTINOL GIVES O-METHYLTAZETTINE METHIODIDE, A COMPOUND IDENTICAL TO THAT OBTAINED FROM THE METHYLATION OF TAZETTINE. THE EPI-MERIC NATURE OF THE ALCOHOLS WAS REALIZED WHEN BOTH COMPOUNDS WERE CONVERTED TO THEIR RESPECTIVE DEOXY DERIVATIVES AND OXIDIZED TO DEOXYTAZETTINONE (13).



THE TAZETTINE STRUCTURE CONTAINS ASYMMETRIC CENTERS AT POSITIONS 3, 4A, 6A AND 12B. THE CONFIGURATION AT EACH OF THESE CARBONS WAS DETERMINED BY STUDYING THE PROPERTIES OF CERTAIN DEGRADATION PRODUCTS.

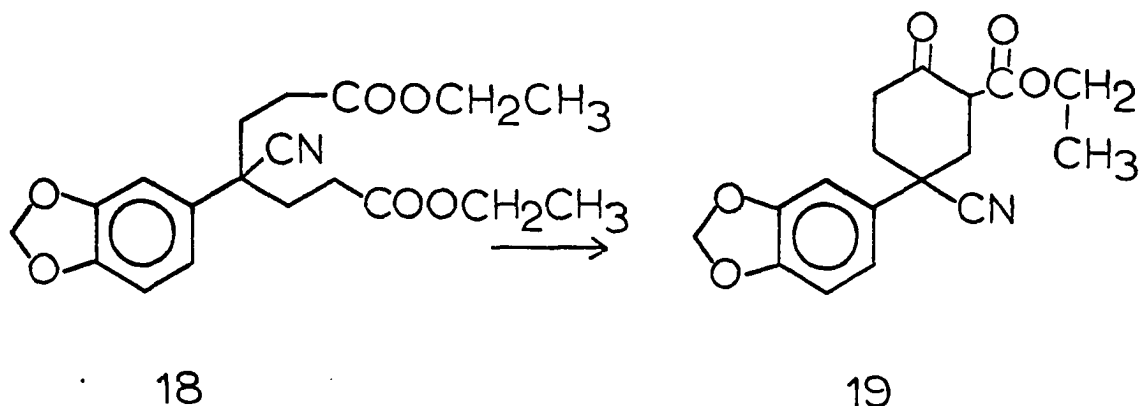


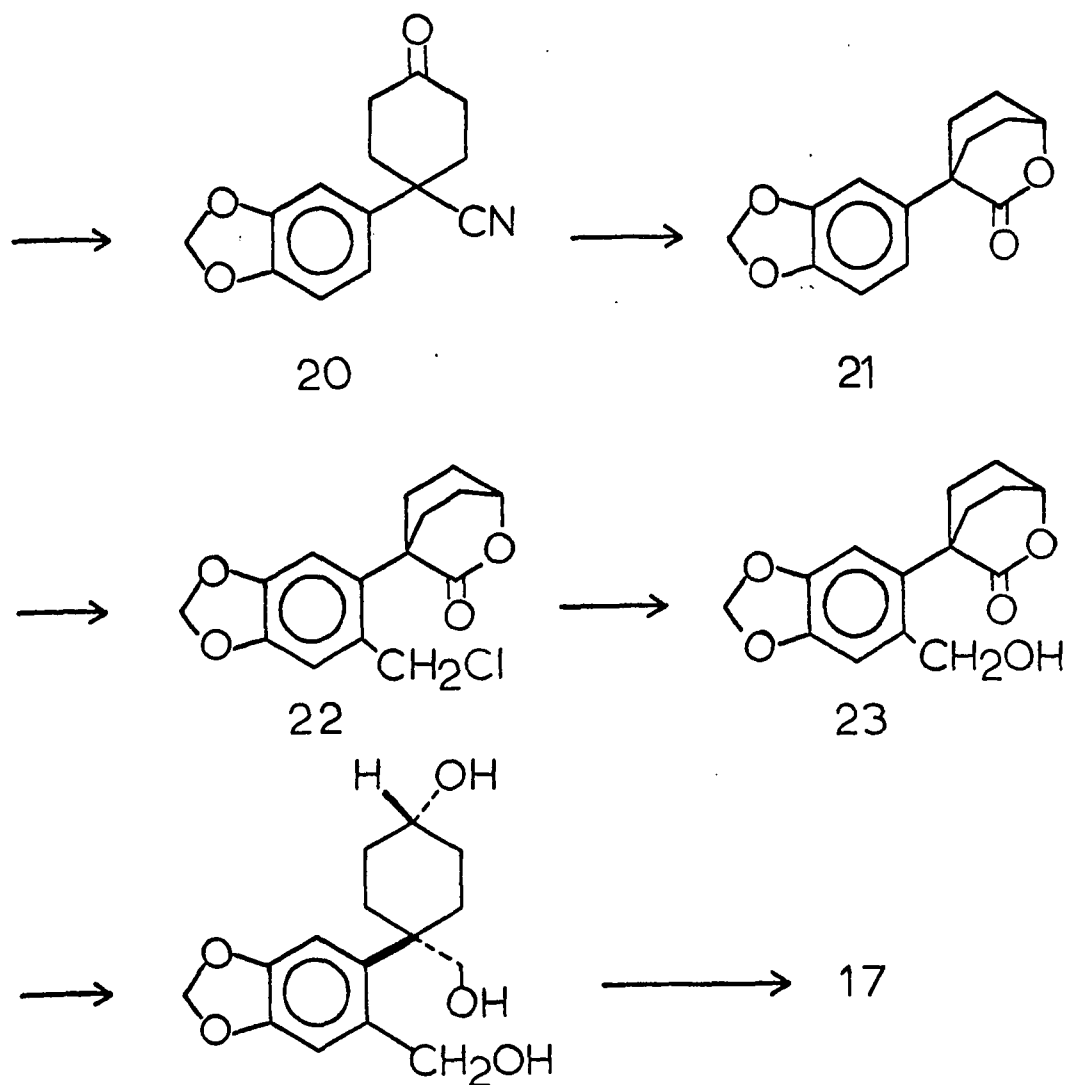
WILDMAN AND HIGHET¹¹ HAD NOTED THAT TAZETTINE IS OXIDIZED TO TAZETTAMIDE (14) WITH MANGANESE DIOXIDE. SIMILARLY IRIE ET AL.¹² CONVERTED ISOTAZETTINOL (12) TO THE AMIDE 15. THIS AMIDE WAS REDUCED TO THE DIHYDRO DERIVATIVE WITH HYDROGEN AND PALLADIUM. LITHIUM ALUMINUM HYDRIDE REDUCTION OF THE AMIDE FOLLOWED BY ACID CYCLIZATION GAVE THE ETHER 16. AN EMDE DEGRADATION OF THE ETHER 16 AFFORDED THE ETHER-ALCOHOL 17. THE PLANE OF SYMMETRY, HENCE OPTICAL INACTIVITY, PROVES THE POSITION OF THE HYDROXYL SUBSTITUTION.



THE ETHER-ALCOHOL 17 WAS SYNTHESIZED TO PROVE THE RELATIVE STEREOCHEMISTRY OF THE 3 AND 12B POSITIONS. THE STARTING MATERIAL FOR THIS SYNTHESIS WAS 3,4-METHYLENEDIOXYBENZYL CYA-

NIDE. CONDENSATION OF THIS ACTIVE METHYLENE COMPOUND WITH TWO MOLES OF ETHYL ACRYLATE GIVES THE DIESTER 18 WHICH BY A DIECKMANN CYCLIZATION AFFORDS THE KETO ESTER 19. HYDROLYSIS AND DECARBOXYLATION GIVES THE CYANO KETONE 20. THE KETONE WAS REDUCED WITH SODIUM BOROHYDRIDE TO GIVE PREDOMINANTLY ONE ALCOHOL. HYDROLYSIS OF THE CYANO GROUP YIELDS A CARBOXYLIC ACID WHICH WAS CYCLIZED TO THE LACTONE 21 UPON HEATING IN ACETIC ANHYDRIDE. CHLOROMETHYLATION OF 21 GIVES THE LACTONE 22 WHICH UPON BASIC HYDROLYSIS FORMS THE BENZYL ALCOHOL 23.¹³ LITHIUM ALUMINUM HYDRIDE REDUCTION OF 23 PRODUCES A TRIOL WHICH WAS CYCLIZED BY ACID TO AN ETHER WHICH WAS IDENTICAL IN ALL RESPECTS TO THE ISOTAZETTINOL DEGRADATION PRODUCT 17. SINCE THE LACTONE 23 OPENS WITH RETENTION OF CONFIGURATION, THE RELATIVE STEREOCHEMISTRY OF THE 3 AND 12B POSITIONS IS ESTABLISHED. THUS THE OXYGEN FUNCTION AT C-3 IS TRANS TO THE AROMATIC RING IN THE ISO SERIES AND THE CORRESPONDING GROUPS MUST BE CIS IN THE NORMAL SERIES. THE RELATIONSHIP BETWEEN THE ISO AND NORMAL SERIES (11 AND 12) HAD ALREADY BEEN ESTABLISHED.





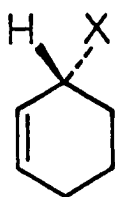
THE CONFIGURATION AT THE 4A POSITION OF TAZETTINE WAS DETERMINED BY BASICITY MEASUREMENTS OF VARIOUS TAZETTINE DERIVATIVES.¹⁰ DEOXYISOTAZETTINOL IS MORE BASIC THAN DEOXYTAZETTINOL BY 1.6 pK_A UNITS. THE GREATER BASICITY OF THE DEOXYISOTAZETTINOL WAS ATTRIBUTED TO HYDROGEN BOND FORMATION BETWEEN THE PROTON OF THE CONJUGATE ACID AND THE HYDROXYL GROUP AT C-3. THIS HYDROGEN BOND CAN FORM ONLY IF THE AMINO GROUP AND HYDROXY

ARE CIS. IT CAN ALSO BE ARGUED THAT A HYDROXYL GROUP CIS TO THE AMINO GROUP WOULD PERMIT A HYDROGEN BOND TO BE FORMED BETWEEN THE HYDROXYL AND NITROGEN, CAUSING THE NITROGEN TO BE LESS BASIC THAN A FREE AMINO GROUP. THUS THE ABOVE ASSIGNMENTS WOULD BE REVERSED IF THIS CONTINGENCY IS SUPPORTED BY HYDROGEN BONDING STUDIES AND THE AMINO GROUP AND HYDROXYL WOULD BE CIS IN DEOXYTAZETTINOL.

IKEDA ET AL.¹⁰ REASONED THAT SINCE THE METHOXYL GROUP OF TAZETTINE IS TRANS TO THE AMINO GROUP BUT CIS TO THE AROMATIC RING, THE C-D RING FUSION MUST BE CIS. THIS STEREOCHEMISTRY REQUIRES THAT THE AMINO GROUP BE QUASI AXIAL, A FEATURE WHICH WOULD FAVOR ITS FACILE ELIMINATION DURING THE HOFMANN DEGRADATION.

THE CONFIGURATION OF THE REMAINING CENTER OF ASYMMETRY (6A) WAS ESTABLISHED BY EXAMINING THE HOFMANN DEGRADATION PRODUCTS OF O-METHYLTAZETTINE. IT WAS SHOWN THAT THE HYDROXYL GROUP OF THE HEMIKETAL MUST BE TRANS TO THE AROMATIC RING.¹² THUS ALL OF THE RELATIVE STEREOCHEMISTRY OF TAZETTINE IS KNOWN.

ONE OF THE MORE USEFUL METHODS FOR DETERMINING ABSOLUTE STEREOCHEMISTRY IS THE APPLICATION OF MILLS' RULE.¹³ THIS RULE HAS GENERAL APPLICATION TO 3-SUBSTITUTED CYCLOHEXENES AND 3-SUBSTITUTED CYCLOPENTENES. A COMPARISON OF THE MOLECULAR ROTATIONS OF SUCH ALLYLIC EPIMERS ENABLES ONE TO TENTATIVELY ASSIGN ABSOLUTE STEREOCHEMISTRY. THUS THE CYCLOHEXENES 18 HAVE BEEN FOUND TO BE MORE DEXTROROTATORY THAN THEIR EPIMERS 19.

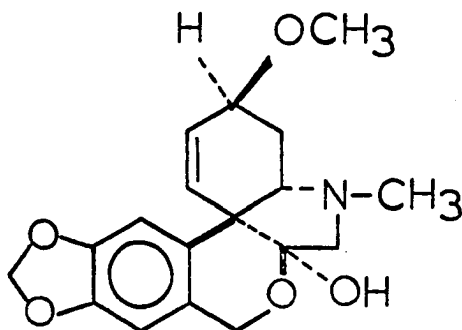


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MILLS' RULE HAS BEEN APPLIED TO A NUMBER OF THE AMARYLLIDACEAE ALKALOIDS¹, P. 355 INCLUDING THE TAZETTINE SERIES¹⁰ AND WHERE THE RELATIVE CONFIGURATIONS ARE KNOWN, THE AGREEMENT IS UNIVERSAL. SINCE THE ISOTAZETTINE DERIVATIVES HAVE MOLECULAR ROTATIONS MORE DEXTROROTATORY THAN THE CORRESPONDING TAZETTINE DERIVATIVES, THE ABSOLUTE STEREOCHEMISTRY OF TAZETTINE TENTATIVELY WAS ASSIGNED THAT DEPICTED IN STRUCTURE 20.^{10*}



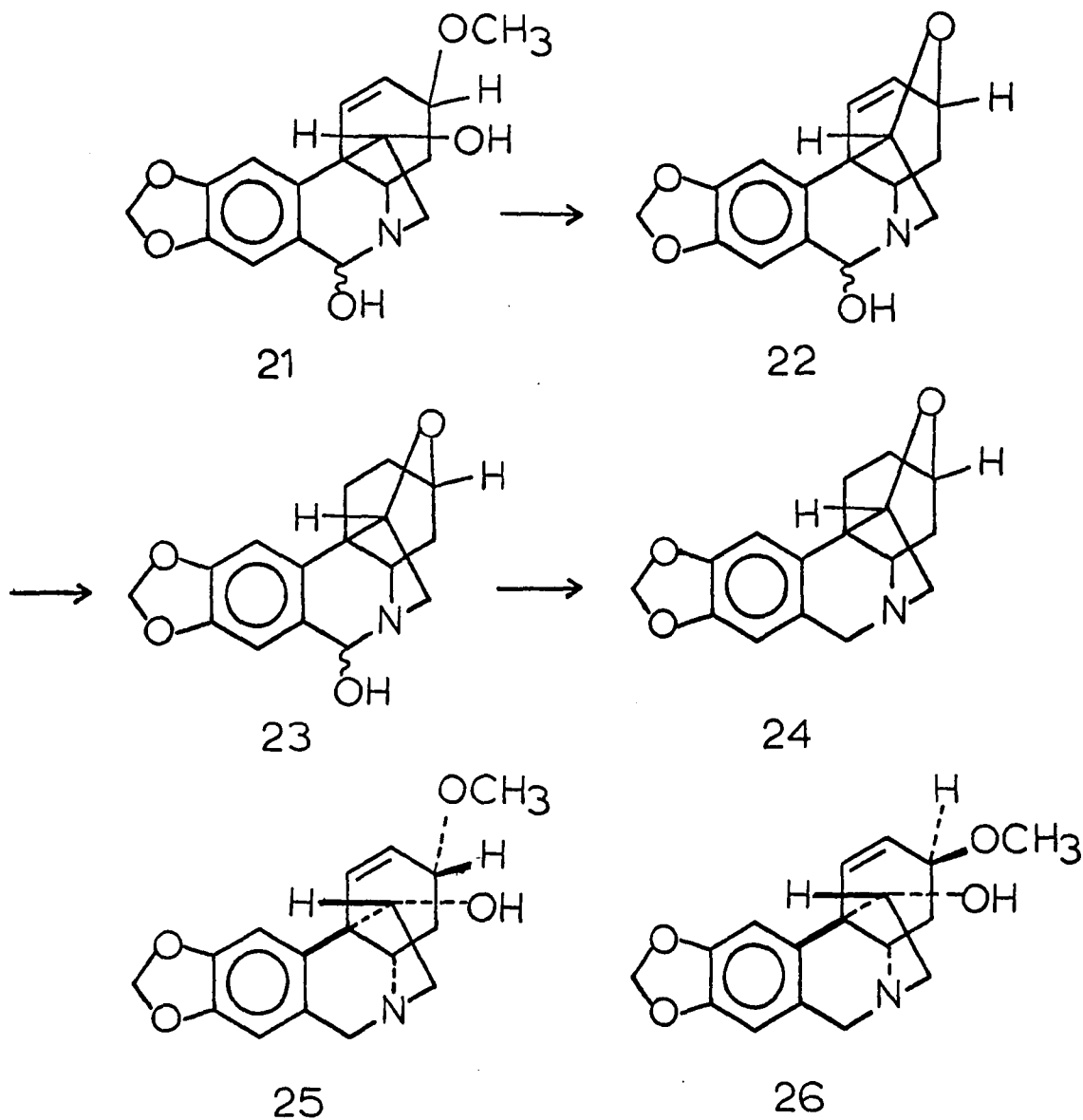
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* ALTHOUGH RECENT EVIDENCE¹⁴ CASTS SOME DOUBT AS TO THE VALIDITY OF MILLS' RULE WHEN APPLIED TO THE AMARYLLIDACEAE ALKALOIDS, THE ABSOLUTE STEREOCHEMISTRY DEPICTED IN STRUCTURE 20 WILL BE USED IN THIS THESIS TO CONFORM WITH THE STRUCTURES PRESENTED IN THE LITERATURE.

HAEMANTHIDINE

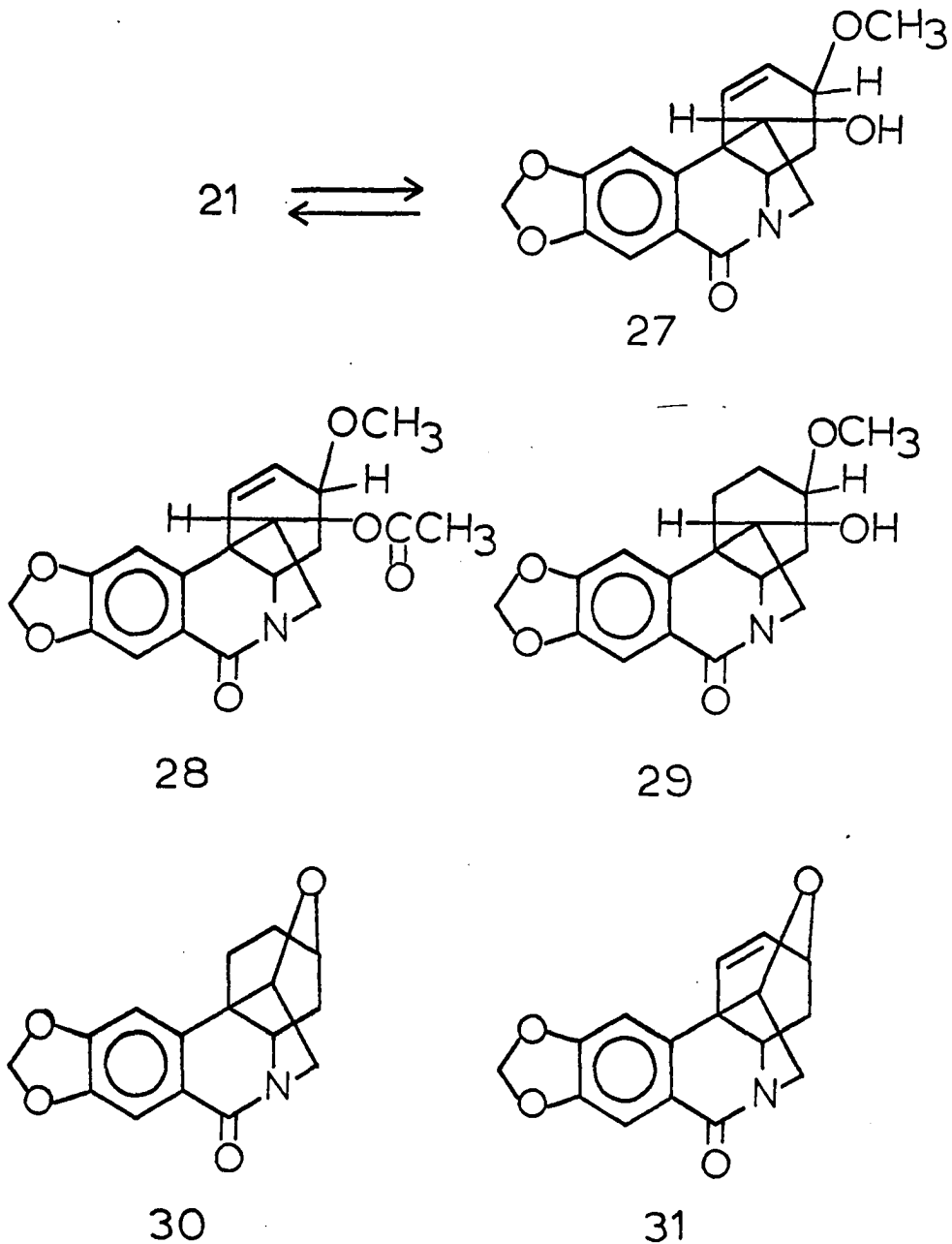
HAEMANTHIDINE, AN ALKALOID ISOLATED FROM NUMEROUS SPECIES OF THE AMARYLLIDACEAE,¹⁵ HAS AN EMPIRICAL FORMULA OF $C_{17}H_{19}NO_5$. AT FIRST HAEMANTHIDINE WAS THOUGHT TO BE N-DEMETHYLTAZETTINE BECAUSE OF ITS FACILE CONVERSION TO TAZETTINE BY N-METHYLATION FOLLOWED BY BASIC HYDROLYSIS.¹⁶ AN ALTERNATIVE STRUCTURE (21) WAS SUGGESTED BY UYEO ET AL.¹⁷ WHEN THE ALKALOID WAS FOUND TO GIVE AN O,O-DIACETATE RATHER THAN THE O,N-DIACETATE ORIGINALLY PROPOSED.¹⁶ TO SUBSTANTIATE THIS STRUCTURE, HAEMANTHIDINE WAS CONVERTED TO A HAEMANTHAMINE DERIVATIVE. UPON HEATING IN STRONG ACID HAEMANTHIDINE LOSES THE ELEMENTS OF METHANOL AND IS CONVERTED TO THE ETHER APOHAEMANTHIDINE (22). APOHAEMANTHIDINE WAS REDUCED TO DIHYDROAPOHAEMANTHIDINE (23) WHICH WAS TREATED WITH THIONYL CHLORIDE AND REDUCED DIRECTLY WITH LITHIUM ALUMINUM HYDRIDE TO DIHYDROAPOHAEMANTHAMINE (24). THE STRUCTURE OF 24 WAS KNOWN FROM THE STRUCTURAL STUDIES OF CRINAMINE AND HAEMANTHAMINE.¹⁸ CRINAMINE AND HAEMANTHAMINE (WHOSE STRUCTURES ARE FIRMLY ESTABLISHED AS 25 AND 26 RESPECTIVELY) ARE BOTH CONVERTED TO 24 UPON ACID HYDROLYSIS AND REDUCTION OF THE DOUBLE BOND.¹⁸ THUS HAEMANTHIDINE MUST BE EITHER A HYDROXYL SUBSTITUTED CRINAMINE OR HAEMANTHAMINE.

THE REMAINING HYDROXYL GROUP OF HAEMANTHIDINE WAS SHOWN TO BE IN THE BENZYLIC POSITION WHEN IT WAS FOUND THAT MANGANESE DIOXIDE CONVERTED THE ALKALOID TO 6-OXOHAEMANTHAMINE (27). THE INFRARED ABSORPTION (5.92 AND 6.12 μ) AND THE ULTRAVIOLET

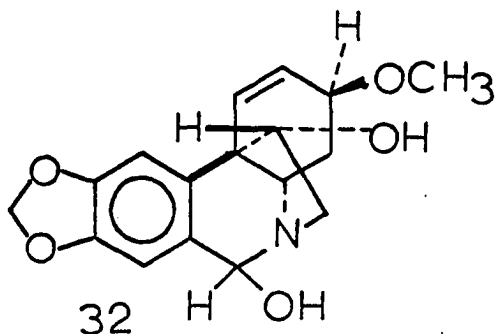


SPECTRUM (MAXIMA AT 323, 268 AND 233 $m\mu$) LEFT LITTLE DOUBT AS TO THE STRUCTURE OF 27. 6-OXOHAEMANTHAMINE WAS REDUCED TO HAEMANTHIDINE WITH EITHER LITHIUM ALUMINUM HYDRIDE OR SODIUM BOROHYDRIDE, A FACT CONSISTENT WITH THE BRIDGEHEAD LACTAM STRUCTURE PROPOSED.

THE PREPARATION AND STRUCTURE PROOF OF 11-ACETYL-6-OXO-HAEMANTHAMINE (28), 6-OXODIHYDROHAEMANTHAMINE (29), 6-OXODIHYDROAPOHAEMANTHAMINE (30) AND 6-OXOAPOHAEMANTHAMINE (31) GAVE FURTHER SUPPORT FOR THE STRUCTURE OF HAEMANTHIDINE AS 21.¹⁷



SINCE HAEMANTHIDINE HAS THE 5,10_B-ETHANOPHENANTHRIDINE RING SYSTEM ITS FACILE CONVERSION TO TAZETTINE MUST INVOLVE A REARRANGEMENT. REGARDLESS OF THE MECHANISM OF THE REARRANGEMENT THE 3 POSITION IS PROBABLY NOT INVOLVED. THUS THE METHOXYL GROUP OF HAEMANTHIDINE MUST BE CIS TO THE AROMATIC RING. THEREFORE HAEMANTHIDINE IS 6-HYDROXYHAEMANTHAMINE AND HAS THE STEREOCHEMISTRY SHOWN IN STRUCTURE 32.

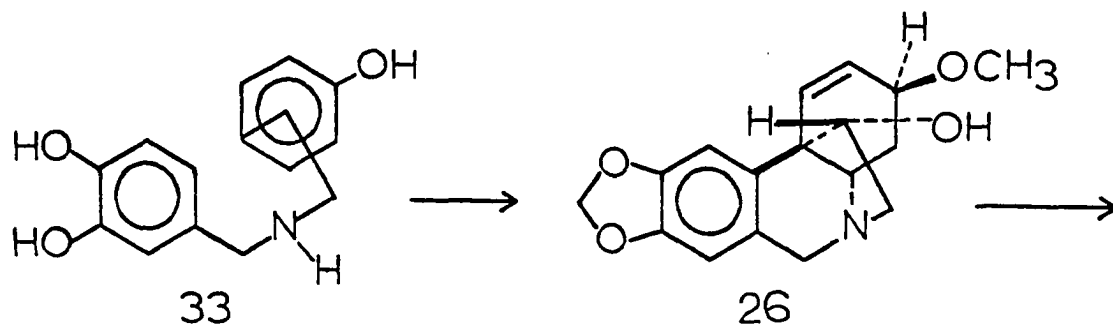


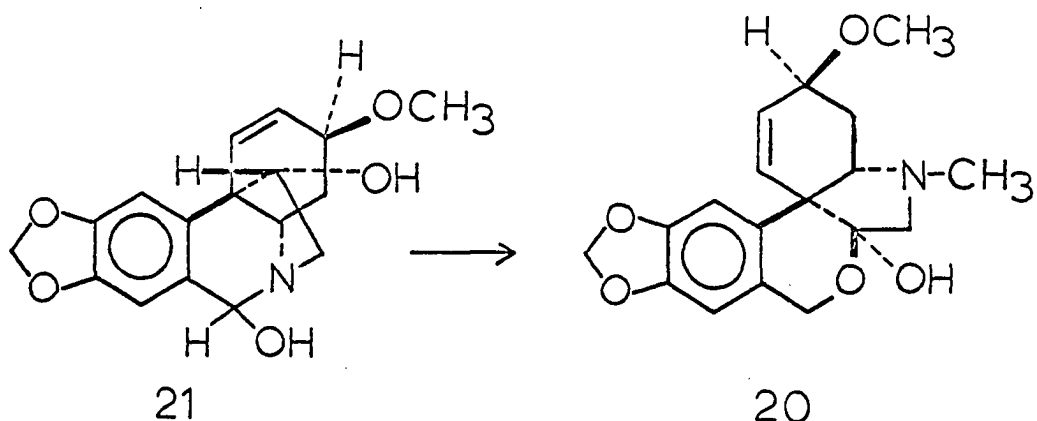
BIOSYNTHESIS OF HAEMANTHIDINE AND TAZETTINE

IN A RECENT PAPER FALES AND WILDMAN¹⁹ DESCRIBED THE BIOSYNTHESIS OF HAEMANTHIDINE AND TAZETTINE. IT WAS REASONED THAT BECAUSE HAEMANTHAMINE IS ISOLATED EARLY IN THE FLOWERING SEASON FROM SPREKELIA FORMOSISSIMA AND TAZETTINE IN LATER COLLECTIONS, THE BIOSYNTHETIC SCHEME OF HAEMANTHAMINE \longrightarrow HAEMANTHIDINE \longrightarrow TAZETTINE SHOULD BE CONSIDERED. IT HAD ALREADY BEEN DETERMINED THAT HAEMANTHAMINE CAN BE DERIVED FROM TYROSINE²⁰ AND PHENYLALANINE.²¹ NORBELLADINE (33)²² HAD ALSO BEEN FOUND TO BE A PRECURSOR TO HAEMANTHAMINE WHICH SUPPORTED THE POSTULATE THAT 5,10_B-ETHANOPHENANTHRIDINE ALKALOIDS ARE FORMED BY A PHENYL-PHENYL OXIDATIVE PROCESS,²³ P. 127 THE PHENYL-PHENYL OXIDATIVE COUPLING MECHANISM CAN NOT BE APPLIED

TO THE BIOSYNTHESIS OF TAZETTINE UNLESS TWO SMALLER FRAGMENTS ARE SIMPLY JOINED TO PRODUCE THE A RING TO C RING BOND. HOWEVER THE SMOOTH IN VITRO TRANSFORMATION OF HAEMANTHIDINE TO TAZETTINE SUGGESTS THAT A SIMILAR BIOSYNTHETIC PATHWAY MAY EXIST IN THE PLANT AS WELL AS A MECHANISM FOR THE HYDROXYLATION OF HAEMANTHAMINE TO GIVE HAEMANTHIDINE.

TO STUDY THIS PROPOSAL SPREKELIA FORMOSISSIMA WAS FED RADIOACTIVE HAEMANTHAMINE. AT SEVERAL STAGES DURING THE GROWING SEASON THE ALKALOIDS WERE ISOLATED AND THEIR RADIOACTIVITY DETERMINED. IT WAS FOUND THAT THE EARLIER COLLECTIONS CONTAINED STRONGLY RADIOACTIVE HAEMANTHAMINE BUT RELATIVELY NON-RADIOACTIVE HAEMANTHIDINE AND TAZETTINE. AS EXPECTED, THE LATER COLLECTIONS CONTAINED RADIOACTIVE HAEMANTHIDINE AND TAZETTINE. TO SHOW THAT THESE CONVERSIONS ARE NOT REVERSIBLE, RADIOACTIVE HAEMANTHIDINE AND TAZETTINE WERE FED TO THE PLANTS IN SEPARATE EXPERIMENTS. IN THE FORMER EXPERIMENT ONLY RADIOACTIVE HAEMANTHIDINE AND TAZETTINE WERE ISOLATED AND IN THE LATTER EXPERIMENT ONLY RADIOACTIVE TAZETTINE WAS OBTAINED. THUS THESE EXPERIMENTS CONFIRMED A BIOSYNTHETIC SEQUENCE LEADING TO TAZETTINE BUT THE INTERCONVERSION MECHANISMS ARE UNKNOWN.



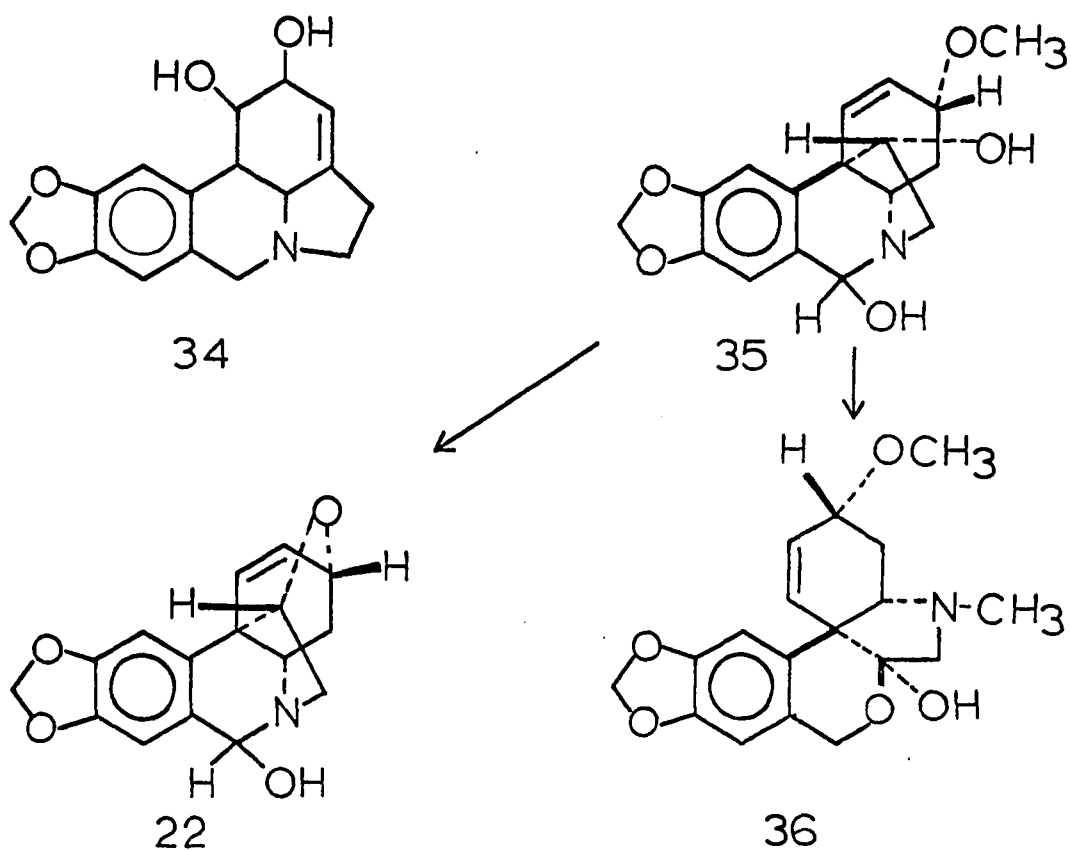


6-HYDROXYCRINAMINE AND CRIWELLINE

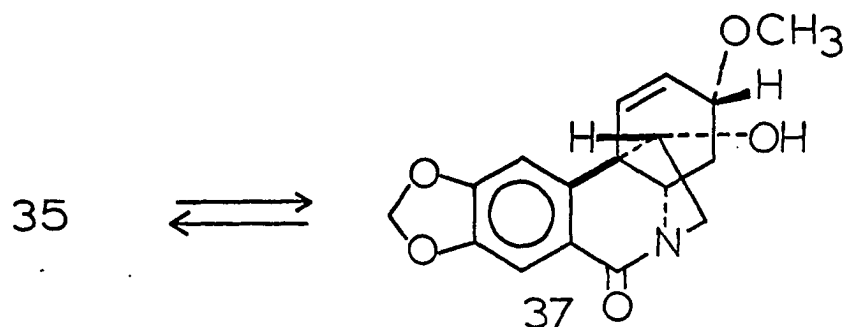
THE STRUCTURES OF 6-HYDROXYCRINAMINE AND CRIWELLINE WERE DEVELOPED SIMULTANEOUSLY AND WILL BE DISCUSSED TOGETHER IN THIS THESIS. BECAUSE OF THE IMPORTANCE OF 6-HYDROXYCRINAMINE IN THIS THESIS, ITS STRUCTURE PROOF AND RELATIONSHIP TO CRIWELLINE, HAEMANTHIDINE AND TAZETTINE WILL BE DISCUSSED IN DETAIL.

FALES, HORN AND WILDMAN²⁴ FIRST REPORTED THE ISOLATION OF 6-HYDROXYCRINAMINE FROM THREE CRINUM SPECIES; CRINUM ZELANDICUM, CRINUM ERUBESCENS AND CRINUM FRIBRIATULUM; ALL COMMONLY REFERRED TO AS "MILK AND WINE LILLIES." IN ADDITION EACH OF THESE SPECIES CONTAINED CRINAMINE (25) AND LYCORINE (34). THE MOLECULAR FORMULA OF 6-HYDROXYCRINAMINE WAS FOUND TO BE $C_{17}H_{19}NO_5$ AND IT CONTAINED ONE METHOXYL GROUP.²⁴ THE ALKALOID WAS OPTICALLY ACTIVE ($[\alpha]_D^{25} + 44^\circ$) AND ABSORBED IN THE ULTRAVIOLET WITH MAXIMA AT 240 $m\mu$ (ϵ 3500) AND 294 $m\mu$ (ϵ 4600). A DIHYDRO DERIVATIVE WAS FORMED UPON CATALYTIC HYDROGENATION WHICH INDICATED THE PRESENCE OF ONE DOUBLE BOND. THE CONVER-

SION OF 6-HYDROXYCRINAMINE TO APOHAEMANTHIDINE UNDER ACIDIC CONDITIONS CONSTITUTES STRONG EVIDENCE THAT 6-HYDROXYCRINAMINE HAS THE STRUCTURE 35, THE C-3 EPIMER OF HAEMANTHIDINE. FURTHER PROOF OF THIS STRUCTURE WAS PRESENTED WHEN IT WAS FOUND THAT 6-HYDROXYCRINAMINE IS CONVERTED TO ISOTAZETTINE (36) UNDER THE SAME CONDITIONS WHICH CONVERT HAEMANTHIDINE TO TAZETTINE. SINCE THE STRUCTURES OF HAEMANTHIDINE, TAZETTINE AND ISOTAZETTINE WERE KNOWN, IT WAS CONCLUDED THAT STRUCTURE 35 MUST REPRESENT 6-HYDROXYCRINAMINE.



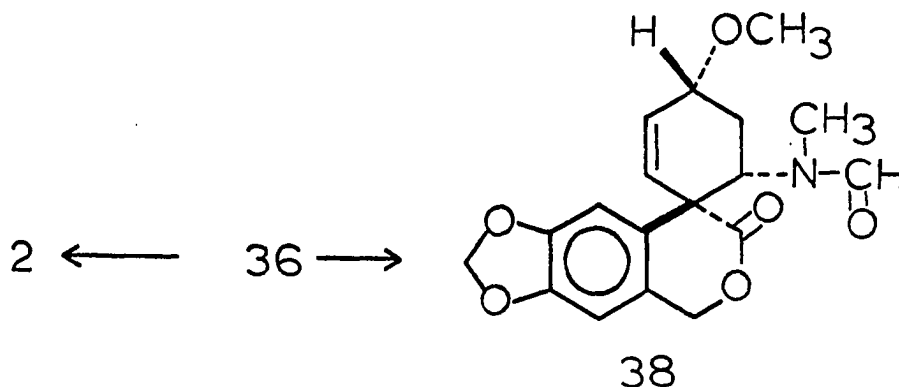
MORE RECENTLY 6-HYDROXYCRINAMINE HAS BEEN ISOLATED FROM AMMOCHARIS CORANICA²⁵ AND HAEMANTHUS NATALENSIS.²⁶ GOOSEN ET AL.²⁶ ALSO CARRIED OUT THE REACTIONS CITED ABOVE FOR 6-HYDROXYCRINAMINE AND IN ADDITION OXIDIZED THE ALKALOID TO THE LACTAM 37 WITH MANGANESE DIOXIDE. IT WAS FOUND THAT 6-OXOCRINAMINE (37) WAS REDUCED TO 6-HYDROXYCRINAMINE WITH LITHIUM ALUMINUM HYDRIDE ANALOGOUS TO THE REDUCTION OF 27 TO HAEMANTHIDINE. THUS GOOSEN ET AL.²⁶ SUGGESTED THAT BOTH REDUCTIONS MUST LEAD TO THE MOST STABLE PRODUCT WITH THE 6-HYDROXYL GROUP IN A PSEUDO EQUATORIAL POSITION, HOWEVER NO STRUCTURE WAS PRESENTED EXPLAINING WHICH CONFIGURATION HAS THE C-6 HYDROXYL GROUP PSEUDO EQUATORIAL. CONSEQUENTLY THE CONFIGURATION OF THE C-6 HYDROXYL GROUP OF BOTH 6-HYDROXYCRINAMINE AND HAEMANTHIDINE REMAINS UNASSIGNED.



THE ISOTAZETTINE CITED ABOVE WAS FOUND TO BE IDENTICAL²⁴ IN ALL RESPECTS TO CRIWELLINE, AN ALKALOID ORIGINALLY ISOLATED FROM CRINUM MOOREI AND CRINUM POWELLII.²⁶ CRIWELLINE WAS FOUND TO CONTAIN A METHOXYL AND A METHYLENEDIOXY GROUP AND THE SAME MOLECULAR FORMULA ($C_{18}H_{21}NO_5$) AS TAZETTINE. A MIXTURE MELTING POINT DETERMINATION OF THE TWO ALKALOIDS SHOWED A DE-

PRESSION, WHICH INDICATED THE ALKALOIDS WERE NOT THE SAME.²⁷

CRIWELLINE (36) IS OXIDIZED TO CRIWELLAMIDE (38) WITH MANGANESE DIOXIDE AND DEGRADED UNDER HOFMANN CONDITIONS TO N,N-DIMETHYL-6-PHENYLPYPERONYL GLYCINATE (2) ANALOGOUS TO THE REACTIONS OF TAZETTINE.²⁸

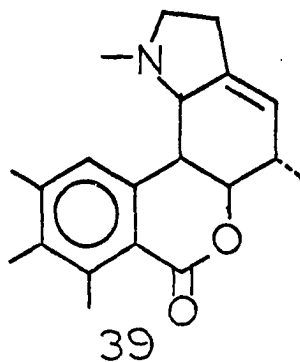


BIOSYNTHESIS OF 6-HYDROXYCRINAMINE AND CRIWELLINE

THE BIOSYNTHESIS OF 6-HYDROXYCRINAMINE AND CRIWELLINE HAS NOT RECEIVED AS MUCH STUDY AS THE BIOSYNTHESIS OF HAEMANTHIDINE AND TAZETTINE. JEFFS²⁹ FOUND THAT TYROSINE CAN BE A PRECURSOR TO 6-HYDROXYCRINAMINE IN HAEMANTHUS NATALENSIS, BUT NO DEGRADATIONS WERE CARRIED OUT TO SHOW THE POSITIONS OF RADIOACTIVITY THAT ORIGINATED WITH 3-C¹⁴-TYROSINE. THE SIMILARITY OF THE CRINAMINE \longrightarrow 6-HYDROXYCRINAMINE \longrightarrow CRIWELLINE PATHWAY TO THE HAEMANTHAMINE \longrightarrow HAEMANTHIDINE \longrightarrow TAZETTINE SCHEME LEADS ONE TO SUSPECT SIMILAR BIOSYNTHETIC TRANSFORMATIONS, BUT NO DATA HAVE BEEN PRESENTED TO SUPPORT SUCH A POSTULATE.

MACRONINE

MACRONINE WAS FIRST ISOLATED BY HAUTH AND STAUFFACHER FROM CRINUM MACRANTHERUM ENGL.⁷ MACRONINE, $C_{18}H_{19}NO_5$, WAS SHOWN TO CONTAIN AN O-METHYL, N-METHYL, METHYLENEDIOXY AND A δ -LACTONE IN CONJUGATION WITH AN AROMATIC RING. THE N.M.R. SPECTRUM SUGGESTED THE PRESENCE OF ONE OLEFINIC PROTON, AN OBSERVATION WHICH INDICATED THAT MACRONINE MAY HAVE THE [2]BENZO-PYRANO[3,4g]INDOLE RING SYSTEM (39).¹, P. 329 ALL AMARYLLIDACEAE ALKALOIDS CONTAINING A LACTONE GROUPING HAVE BEEN FOUND TO CONTAIN THIS RING SYSTEM.



METHODS OF STRUCTURE ELUCIDATION

THE STRUCTURES OF THE AFOREMENTIONED COMPOUNDS HAVE BEEN INVESTIGATED PRIMARILY BY CLASSICAL CHEMICAL METHODS SUPPLEMENTED BY INFRARED AND ULTRAVIOLET SPECTROSCOPY. PURITY WAS DETERMINED BY MICROANALYSIS, COLUMN CHROMATOGRAPHY AND MELTING POINT. WITH THE EXCEPTION OF MACRONINE, NO N.M.R. OR MASS SPECTRAL EVIDENCE HAS BEEN PRESENTED IN SUPPORT OF THE STRUCTURES PROPOSED FOR THESE COMPOUNDS AT THE TIME THE WORK DESCRIBED IN THIS THESIS WAS INITIATED.

RESULTS AND DISCUSSION

6-HYDROXYCRINAMINE AND HAEMANTHIDINE

HAEMANTHIDINE IS PRESENT IN A NUMBER OF AMARYLLIDACEAE SPECIES BUT IN SMALL AMOUNTS.^{1, p. 370} HAEMANTHUS NATALENSIS CONTAINS HAEMANTHIDINE IN GREATER QUANTITIES, HOWEVER THIS PLANT IS NOT AVAILABLE IN THIS COUNTRY. 6-HYDROXYCRINAMINE IS READILY AVAILABLE FROM CRINUM ERUBESCENS²³ A SPECIES THAT GROWS ABUNDANTLY IN THE SOUTHERN PART OF THE UNITED STATES. FOR THESE REASONS 6-HYDROXYCRINAMINE WAS THE ALKALOID OF CHOICE FOR MOST OF THE STUDIES DESCRIBED IN THIS THESIS.

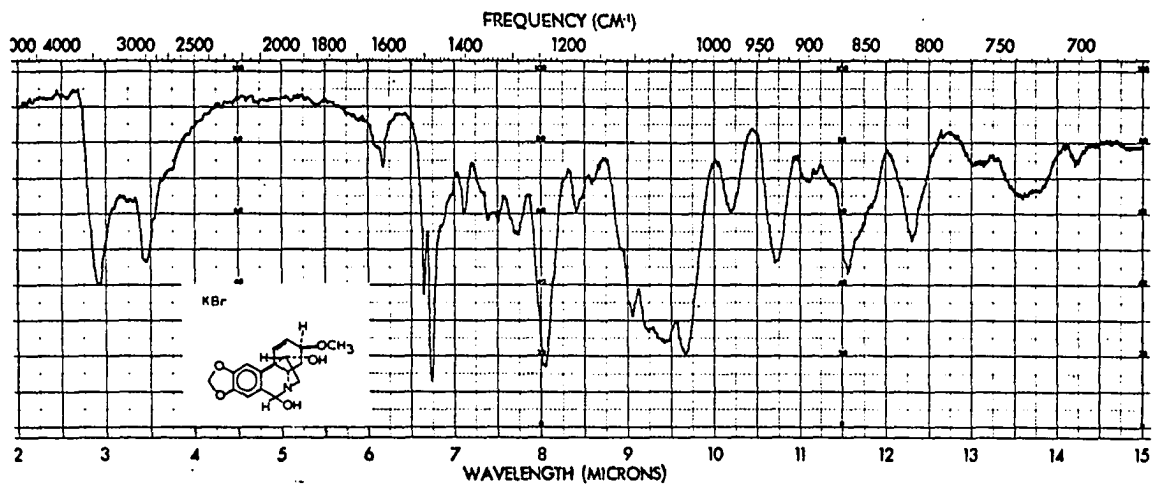
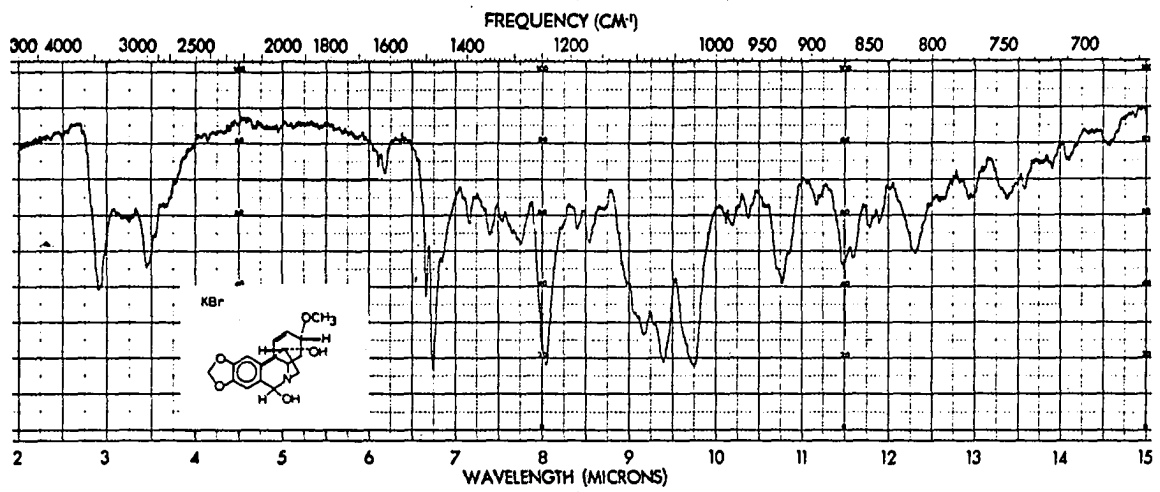
THE CRUDE ALKALOID EXTRACT OF C. ERUBESCENS WILL CONTAIN 45-50 % 6-HYDROXYCRINAMINE, 40-45 % LYCORINE AND LESSER AMOUNTS OF CRINAMINE, CRIWELLINE, ACETYLCARANINE AND CORANICINE. 6-HYDROXYCRINAMINE IS READILY IDENTIFIED BY ITS INFRARED SPECTRUM (FIG. 1A) AND ITS PURITY CAN BE ESTIMATED BY THIN LAYER CHROMATOGRAPHY (T.L.C.). WHEREAS MOST OF THE AMARYLLIDACEAE ALKALOIDS CAN BE EXAMINED FOR PURITY BY GAS CHROMATOGRAPHY, 6-HYDROXYCRINAMINE UNDERWENT DECOMPOSITION UNDER SIMILAR CONDITIONS.

DURING THE INITIAL STAGES OF THE STUDY OF 6-HYDROXYCRINAMINE AND RELATED COMPOUNDS, IT WAS DECIDED THAT A N.M.R. SPECTRUM WOULD BE USEFUL FOR STRUCTURAL VERIFICATION AS WELL AS REFERENCE PURPOSES. INITIAL EXAMINATION OF THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE HOWEVER, REVEALED IRREGULARITIES IN THE AROMATIC AND BENZYLIC PROTON REGIONS OF THE SPEC-

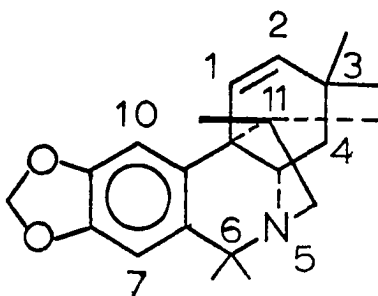
FIG. 1: INFRARED SPECTRA

A: 6-HYDROXYCRINAMINE (35)

B: HAEMANTHIDINE (32)

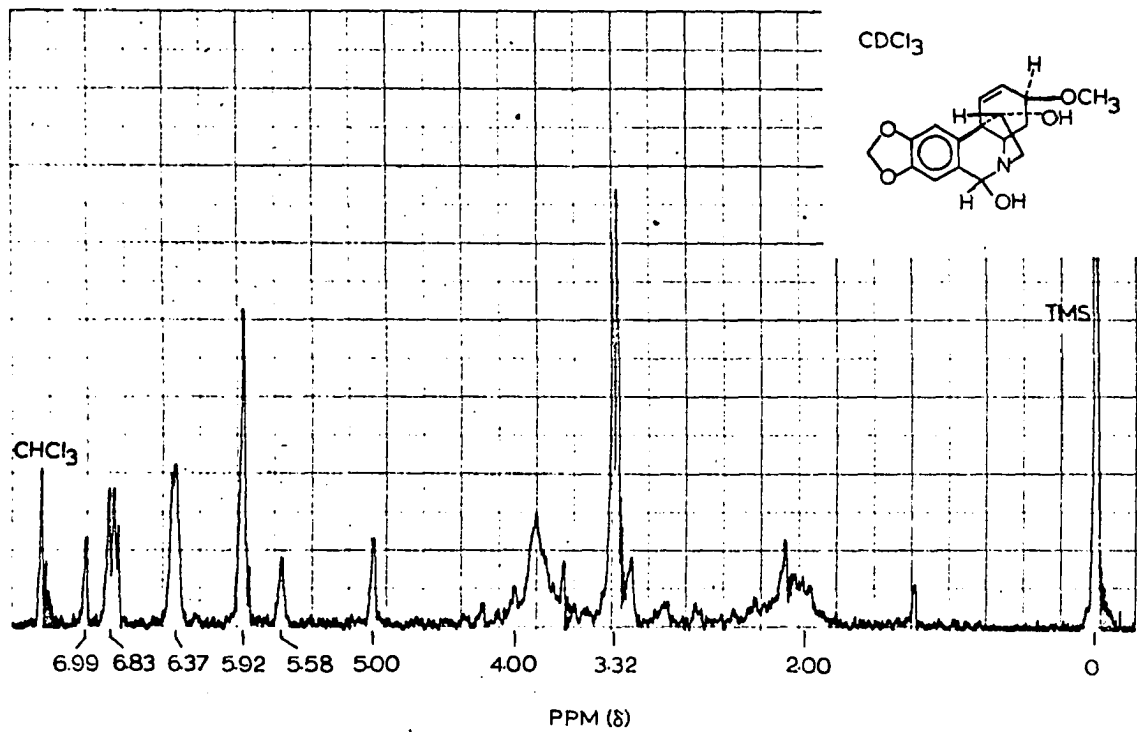
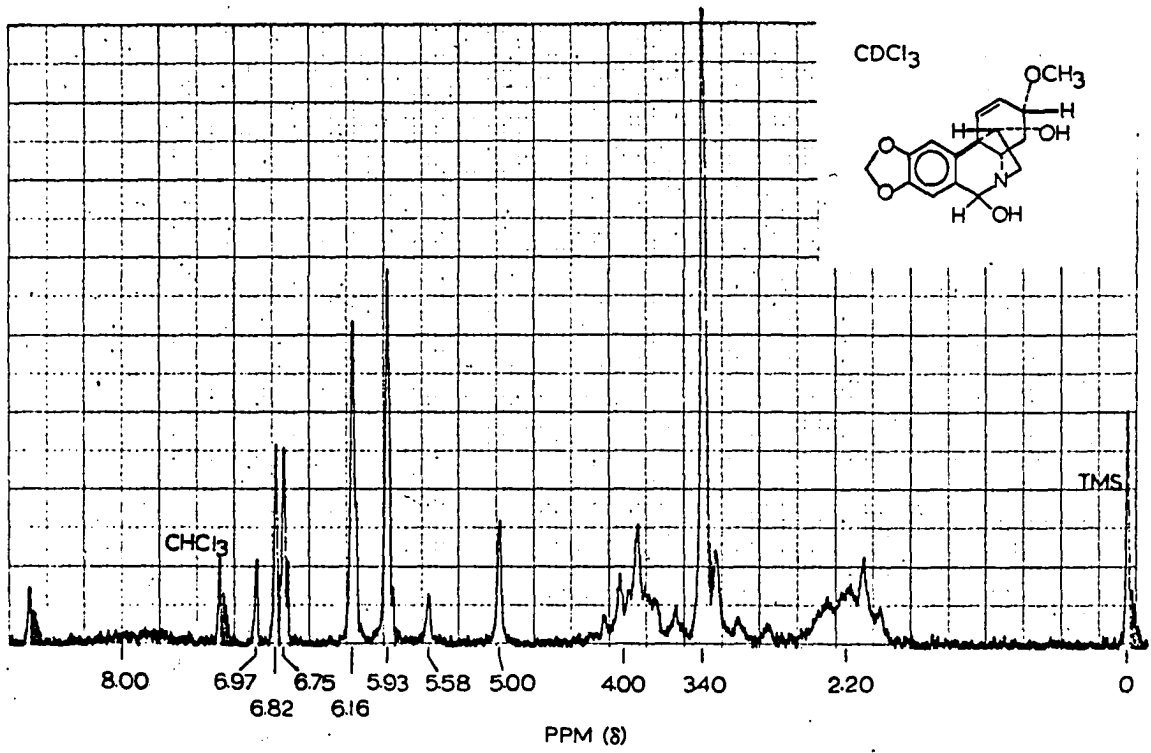


TRUM. THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE IN DEUTERIO-CHLOROFORM (FIG. 2A) SHOWS SEVERAL PEAKS IN THE PART OF THE SPECTRUM (6.7 - 7.3 P.P.M.) ORDINARILY OCCUPIED BY AROMATIC PROTONS. A PRIORI ONE WOULD EXPECT TWO SINGLETS FOR THE AROMATIC PROTONS. THE OLEFINIC PROTONS PRODUCE A NEAR SINGLET AT 6.16 P.P.M. AND THE SINGLET AT 5.93 P.P.M. IS ASSIGNED TO THE METHYLENEDIOXY PROTONS. EITHER OF THE TWO PEAKS AT 5.58 OR 5.00 P.P.M. COULD BE ASSIGNED TO THE BENZYLIC PROTON RESONANCE, BUT NEITHER PEAK AREA INTEGRATES FOR ONE PROTON. THE COMPLEX MULTIPLY AT 4.00 P.P.M. PROBABLY CONSISTS OF THE PEAKS PRODUCED BY PROTONS AT POSITIONS 3, 11 AND 4A. THE METHOXYL GROUP GIVES RISE TO A THREE PROTON SINGLET AT 3.40 P.P.M. AND THE PROTONS AT C-4 ARE ASSIGNED TO THE PEAKS CENTERED AT 2.20 P.P.M. WHEN THE SAMPLE WAS SHAKEN WITH DEUTERIUM OXIDE THE BROAD PEAK AT 8.00 P.P.M. AND PART OF THE MULTIPLY AT 2.20 P.P.M. DISAPPEARED, WHICH INDICATED THESE TO BE HYDROXYL PROTON RESONANCES.



IN A RECENT PAPER, HAUGWITZ, JEFFS AND WENKERT³⁰ REPORTED AND INTERPRETED THE N.M.R. SPECTRA OF A NUMBER OF AMARYL-

FIG. 2: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: 6-HYDROXYCRINAMINE (35)
B: HAEMANTHIDINE (32)



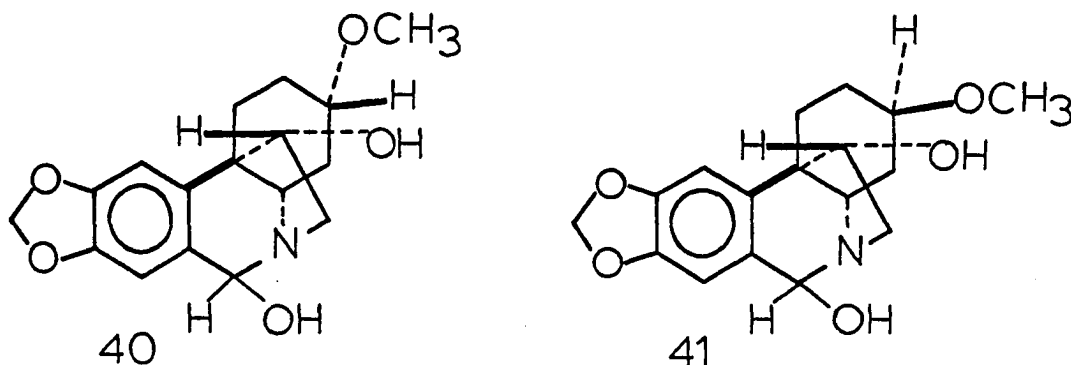
LIDACEAE ALKALOIDS. SEVERAL OF THE ALKALOIDS EXAMINED BY THESE WORKERS ARE THE SUBJECTS OF THIS THESIS AND THEIR SPECTRA ARE ALSO DISCUSSED HERE. ALTHOUGH THIS AUTHOR AGREES WITH THE FINDINGS OF THESE AUTHORS IN MANY RESPECTS, SEVERAL ASSIGNMENTS APPEAR TO BE IN ERROR AND THE IRREGULARITIES NOTED IN THE SPECTRUM OF 6-HYDROXYCRINAMINE ARE NOT MENTIONED.

SINCE IRREGULARITIES WERE NOTED IN THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE, THE FIRST PROBABLE CAUSE I. E. IMPURITIES, WAS INVESTIGATED. HOWEVER, BY ALL METHODS AVAILABLE TO THIS AUTHOR, I. E. THIN LAYER CHROMATOGRAPHY, COLUMN CHROMATOGRAPHY AND MELTING POINT, THE SAMPLE WAS PURE. IN ADDITION, ALL CHEMICAL REACTIONS OF 6-HYDROXYCRINAMINE PROCEED AS IF ONLY ONE COMPONENT WAS PRESENT.

IF THIS PHENOMENON IS A PROPERTY OF THE MOLECULE AND NOT AN IMPURITY THEN HAEMANTHIDINE (32) SHOULD EXHIBIT A SIMILAR SPECTRUM. INDEED THE N.M.R. SPECTRUM OF 32 (FIG. 2B) IS VERY SIMILAR TO THAT OF 6-HYDROXYCRINAMINE EXCEPT THAT THE PEAKS AT 5.58 AND 6.99 P.P.M. ARE PROPORTIONATELY LARGER. THESE DATA LED TO THE CONCLUSION THAT THE SPECTRA OBSERVED IS REPRESENTATIVE OF THE ALKALOIDS AND NOT OF CONTAMINANTS. SINCE AN EXPLANATION FOR THESE PEAKS WAS NOT AVAILABLE, IT WAS DECIDED TO INVESTIGATE THE PHENOMENA IN DETAIL. A NUMBER OF DERIVATIVES OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE WERE SYNTHESIZED AND THEIR N.M.R. SPECTRA OBTAINED. THE PREPARATION OF THESE DERIVATIVES IS DESCRIBED BELOW AND A DISCUSSION OF THEIR N.M.R. SPECTRA IS PRESENTED LATER.

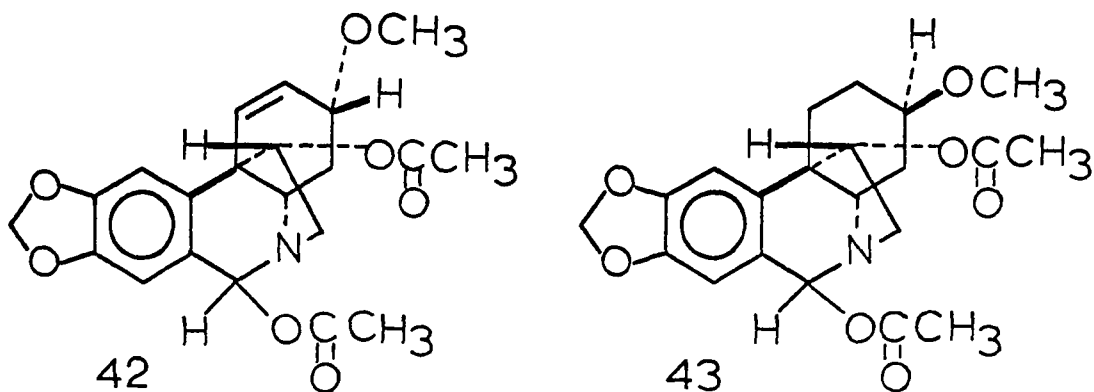
PREPARATION OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE DERIVATIVES

6-HYDROXYCRINAMINE AND HAEMANTHIDINE FORM DIHYDRO DERIVATIVES (40 AND 41, RESPECTIVELY) UPON CATALYTIC HYDROGENATION. THESE COMPOUNDS ARE CRYSTALLINE, HIGH MELTING AND HOMOGENEOUS BY T.L.C.^{24, 16} THE INFRARED SPECTRA SHOW STRONG HYDROXYL ABSORPTION AT $2.8 - 3.2\mu$.

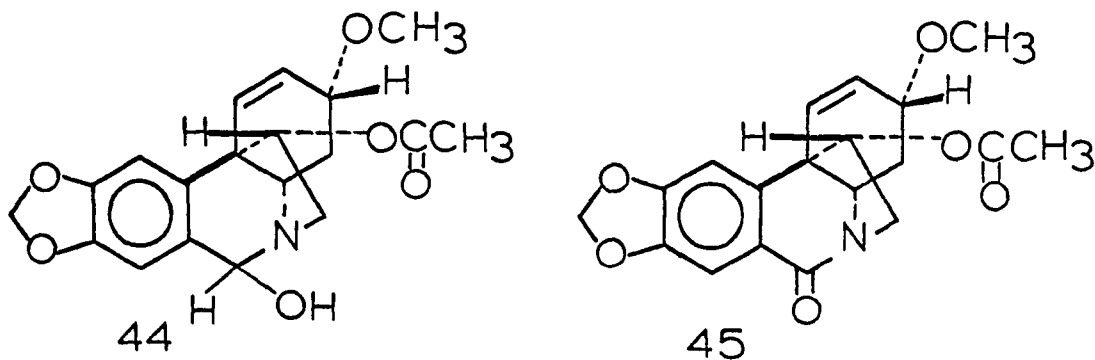


ACETIC ANHYDRIDE IN PYRIDINE CONVERTS 6-HYDROXYCRINAMINE AND HAEMANTHIDINE TO THEIR RESPECTIVE DIACETATES. 6,11-DIACETYL-6-HYDROXYCRINAMINE (42)²⁶ IS NOT CRYSTALLINE, BUT IT CAN BE PURIFIED BY DISTILLATION AND ITS HOMOGENEITY DETERMINED BY T.L.C. STRONG CARBONYL ABSORPTION APPEARED IN THE INFRARED (5.74μ) AND HYDROXYL ABSORPTION IS ABSENT. 6,11-DIACETYL-6-HYDROXYCRINAMINE CAN BE HYDROLYZED UNDER BASIC CONDITIONS OR REDUCED WITH LITHIUM ALUMINUM HYDRIDE TO A COMPOUND IDENTICAL IN ALL RESPECTS WITH 6-HYDROXYCRINAMINE. 6,11-DIACETYL-HAEMANTHIDINE (43) IS CRYSTALLINE, HIGH MELTING AND HOMOGENEOUS BY T.L.C. THE INFRARED SPECTRUM SHOWS THE EXPECTED CARBONYL ABSORPTION AT 5.73μ .

11-ACETYL-6-HYDROXYCRINAMINE (44) IS FORMED AS A PRODUCT



OF INCOMPLETE ACETYLATION DURING THE PREPARATION OF 42. THIS COMPOUND IS CRYSTALLINE AND ABSORBS IN THE INFRARED AT 5.76μ (FIG. 3A). A BROAD HYDROXYL BAND IS ALSO PRESENT IN THE INFRARED IN THE $2.9 - 3.2\mu$ REGION. THE POSITION OF THE ACETYL GROUP WAS PROVEN BY THE OXIDATION OF 44 WITH MANGANESE DIOXIDE TO THE LACTAM 45. THE LACTAM ABSORBED IN THE INFRARED AT 5.75 AND 5.91μ (FIG. 3B), AND IN THE ULTRAVIOLET AT 232 , 277 AND $321 m\mu$. LITHIUM ALUMINUM HYDRIDE REDUCTION OF 45 YIELDS 6-HYDROXYCRINAMINE AS THE ONLY PRODUCT.



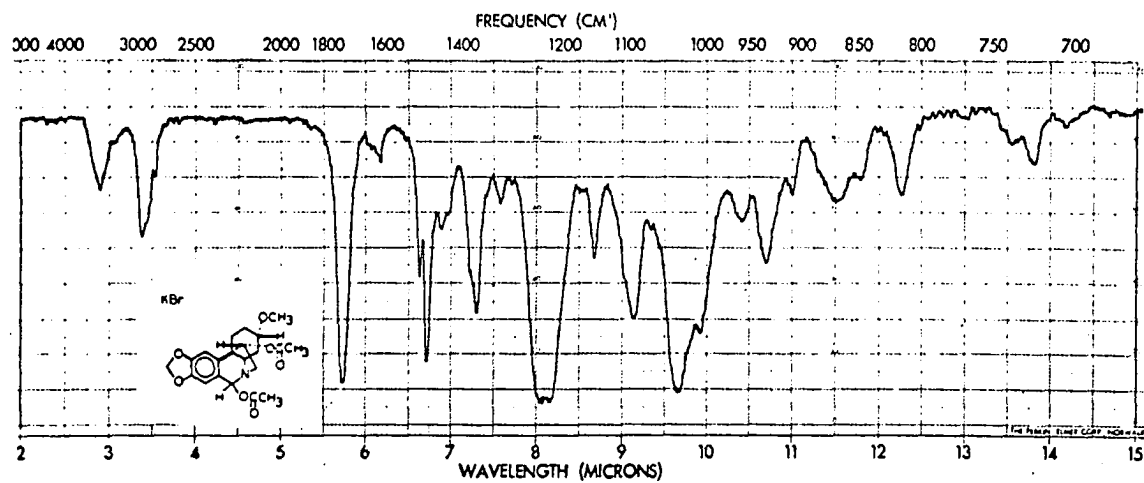
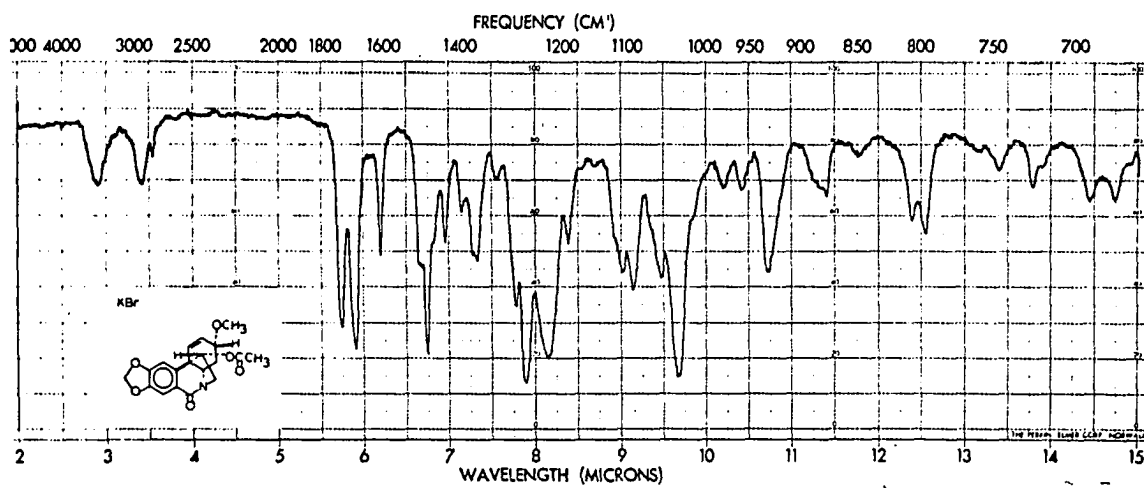
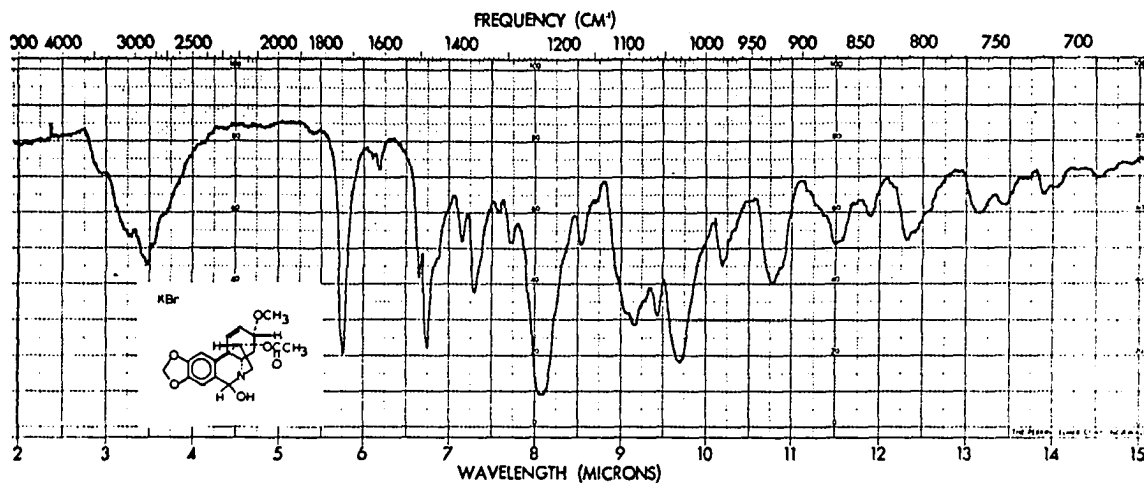
6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46) AND 6,11-DIACETYLDIHYDROHAEMANTHIDINE (47) ARE PREPARED BY THE ACETYLATION OF THE CORRESPONDING DIHYDRO ALKALOIDS. 6,11-DIACETYLDIHYDRO-

FIG. 3: INFRARED SPECTRA

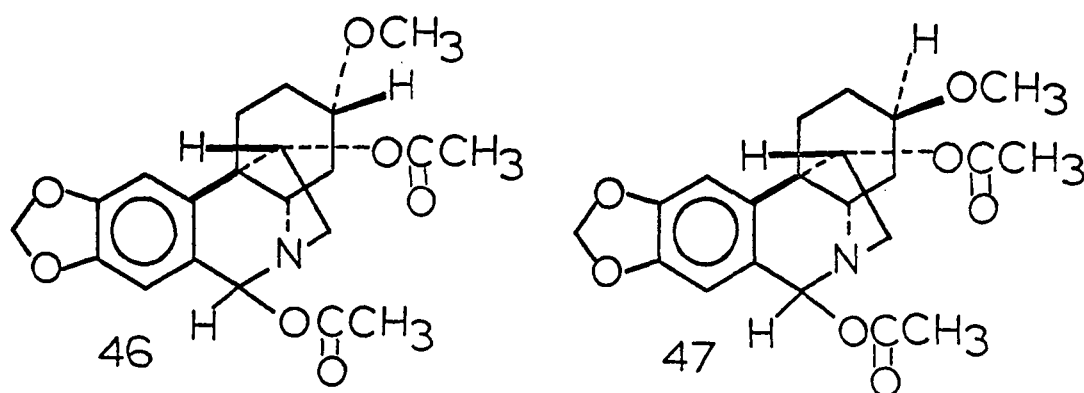
A: 11-ACETYL-6-HYDROXYCRINAMINE (44)

B: 11-ACETYL-6-OXOCRINAMINE (45)

C: 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE
(46)



6-HYDROXYCRINAMINE IS NOT CRYSTALLINE, BUT IT CAN BE PURIFIED BY COLUMN CHROMATOGRAPHY AND DISTILLATION. NO HYDROXYL ABSORPTION IS PRESENT IN THE INFRARED, HOWEVER A CARBONYL STRETCHING BAND IS EVIDENT AT 5.74μ (FIG. 3C). 6,11-DIACETYLDIHYDRO-HAEMANTHIDINE IS A CRYSTALLINE, HIGH MELTING COMPOUND AND HOMOGENEOUS BY T.L.C. A CARBONYL PEAK APPEARS IN THE INFRARED AT 5.74μ (FIG. 4A).



11-ACETYLDIHYDRO-6-HYDROXYCRINAMINE (48) MAY BE PREPARED IN QUANTITATIVE YIELD BY HYDROGENATION OF 6,11-DIACETYL-6-HYDROXYCRINAMINE IN ACETIC ACID. THIS DERIVATIVE ABSORBS IN THE INFRARED AT 5.74μ (FIG. 4B) AND IN THE ULTRAVIOLET AT 237 AND 288 $m\mu$. THE COMPOUND IS CRYSTALLINE AND PURE BY T.L.C.

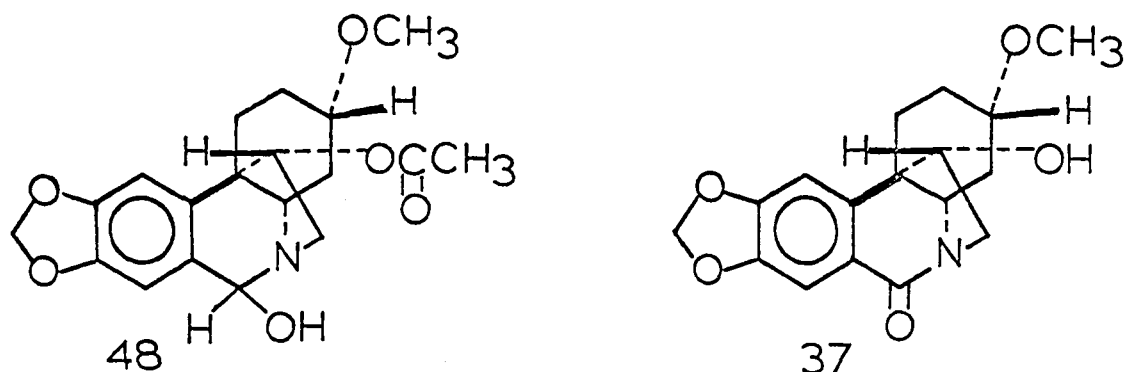
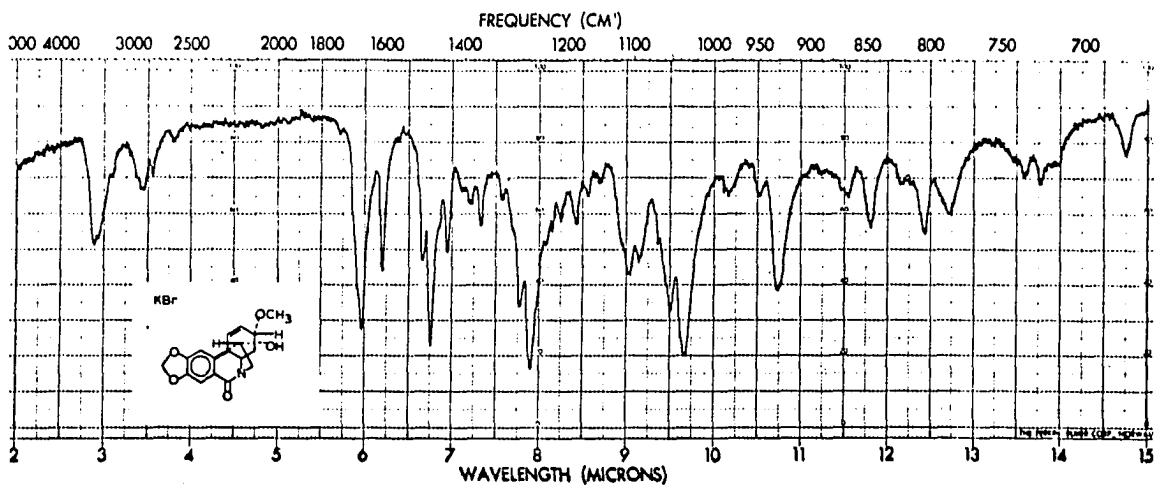
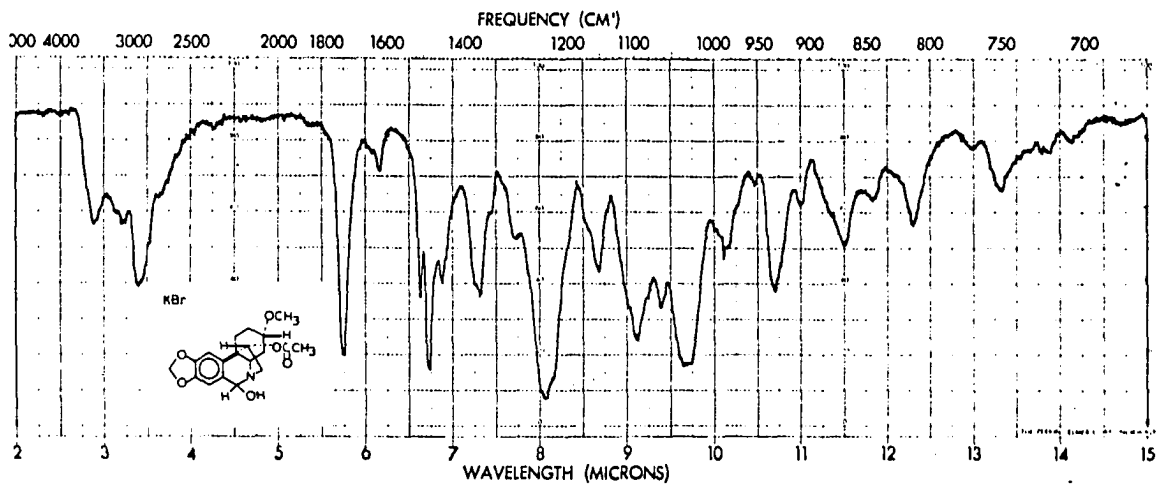
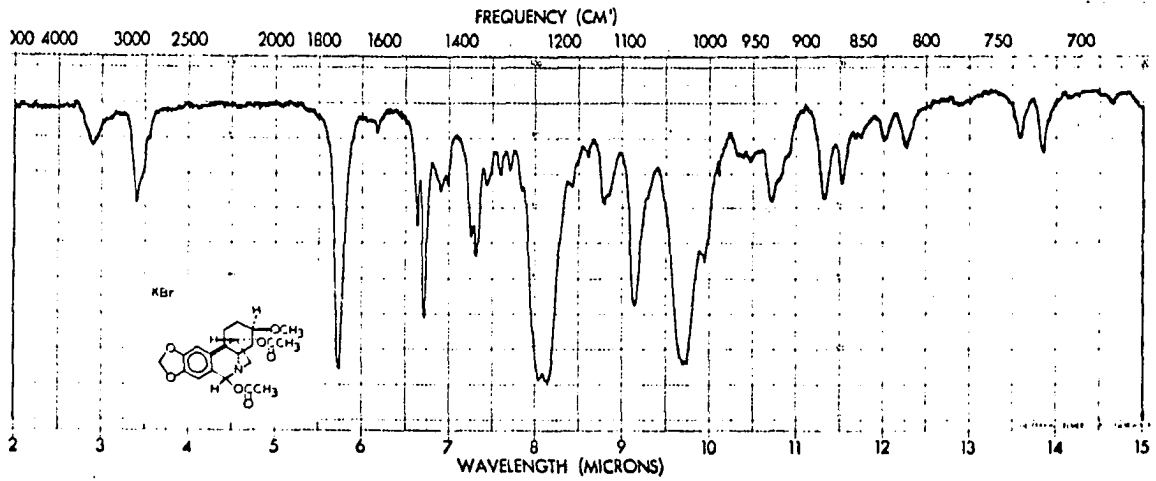


FIG. 4: INFRARED SPECTRA

A: 6,11-DIACETYLDIHYDROHAEMANTHIDINE (47)

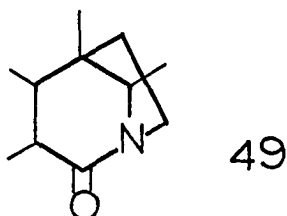
B: 11-ACETYLDIHYDRO-6-HYDROXYCRINAMINE (48)

C: 6-OXOCRINAMINE (37)

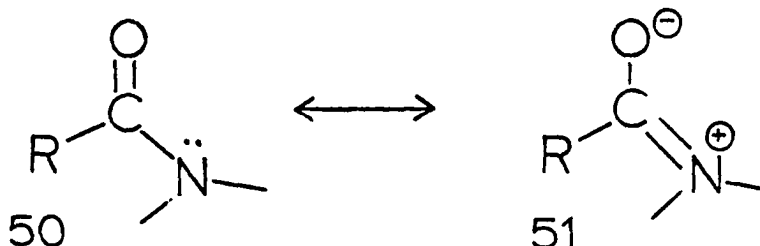


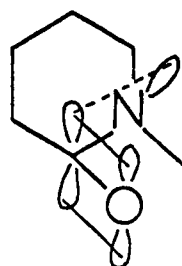
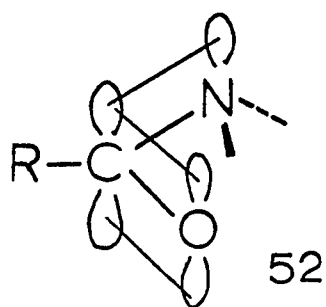
6-HYDROXYCRINAMINE AND HAEMANTHIDINE ARE READILY OXIDIZED TO 6-OXOCRINAMINE (37) AND 6-OXOHAEMANTHAMINE (27), RESPECTIVELY. 6-OXOCRINAMINE HAS CARBONYL ABSORPTION IN THE INFRARED AT 5.97μ (FIG. 4C) AND ULTRAVIOLET ABSORPTION AT 232, 274 AND $323\text{ m}\mu$. THIS SPECTRAL EVIDENCE SUPPORTS THE PROPOSED STRUCTURE.

INHERENT IN THE STRUCTURES OF 27 AND 37 IS THE 1-AZABICYCLO[3,2,1]OCTANE UNIT (49). THIS UNIT IS REGARDED AS UNUSUAL BECAUSE ITS PROPERTIES CORRESPOND TO THOSE OF AN AMINO KETONE RATHER THAN AN AMIDE. THIS PECULIARITY CAN BEST BE EXPLAINED WITH A MODERN INTERPRETATION³¹ OF BREDT'S RULE.³² IN NORMAL

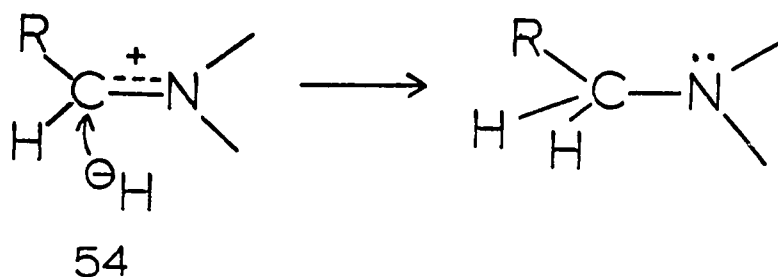
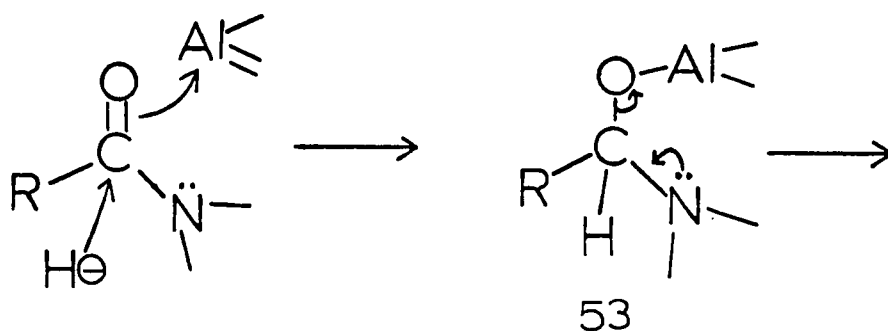


LACTAMS AND AMIDES THE ELECTRONS IN THE P ORBITAL OF NITROGEN INTERACT WITH THE CARBONYL GROUP TO AN EXTENT THAT THE RESONANCE FORMS 50 AND 51 ARE BOTH IMPORTANT. THE CONTRIBUTION OF 51 IS GREATEST IN AMIDES WHERE THERE IS FREE ROTATION ABOUT THE NITROGEN-CARBONYL CARBON BOND WHICH ALLOWS THE GROUPS TO ORIENT THEMSELVES IN SUCH A MANNER THAT MAXIMUM OVERLAP OF ORBITALS IS ACHIEVED (SEE 52). IN NORMAL LACTAMS THIS OVERLAP

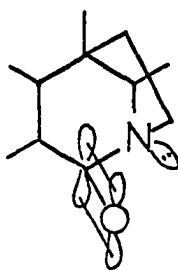




IS REDUCED SLIGHTLY, BUT SIGNIFICANT INTERACTION CAN STILL BE ACHIEVED. AMIDES AND NORMAL LACTAMS SHOW THE EFFECT OF THIS ORBITAL OVERLAP WHEN THEY ARE REDUCED TO AMINES WITH LITHIUM ALUMINUM HYDRIDE.³³ IN THE FIRST STEP A HYDRIDE ION ATTACKS THE CARBONYL CARBON TO GIVE THE COMPLEX 53. THE METAL OXIDE COMPLEX IS LOST, LEAVING A POSITIVE CHARGE DISTRIBUTED BETWEEN THE CARBON AND NITROGEN (SEE 54). THE IMMINIUM ION (54) IS SUBSEQUENTLY REDUCED BY ANOTHER HYDRIDE ION TO THE AMINE.

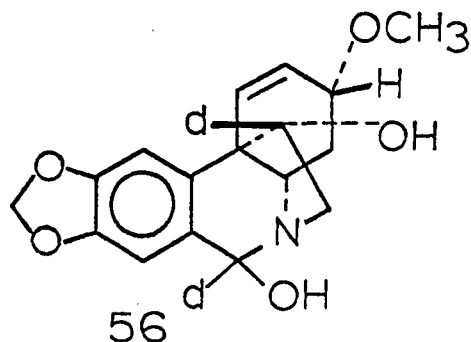
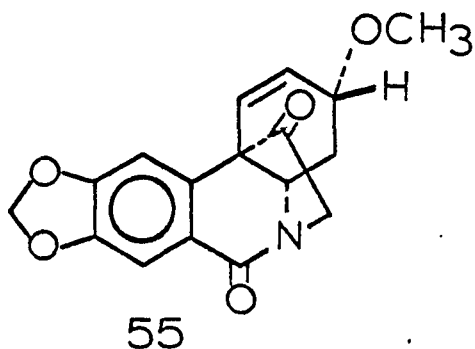


THE RIGIDITY OF THE 1-AZABICYCLO[3,2,1]OCTANE RING SYSTEM PREVENTS THE NITROGEN P ORBITAL FROM ALLIGNING WITH THE CARBONYL π BOND. THUS THE CONTRIBUTION OF FORM 51 IN BRIDGEHEAD LACTAMS IS MINIMAL. BECAUSE OF THIS SMALL AMOUNT OF ORBITAL OVERLAP, THE CARBONYL GROUP REACTS AS IF IT WERE A KETONE. THE REACTION PRODUCT OF THE REDUCTION OF 6-OXOCRINAMINE WITH LITHIUM ALUMINUM HYDRIDE IS 6-HYDROXYCRINAMINE. 6-HYDROXYCRINAMINE IS THE EXPECTED PRODUCT BECAUSE AFTER INITIAL HYDRIDE ATTACK TO GIVE THE COMPLEX 53, ELIMINATION OF THE OXIDE IS NOT POSSIBLE AS THE IMMINIUM ION CANNOT BE FORMED. THUS THE REACTION STOPS AFTER THE FIRST STEP.



ALL ATTEMPTS TO OXIDIZE 6-HYDROXYCRINAMINE TO 6,11-DIOXOCRINAMINE WERE UNSUCCESSFUL AND EVEN THE OXIDATION OF 6-OXOCRINAMINE TO 6,11-DIOXOCRINAMINE PROCEEDED ONLY UNDER VERY MILD CONDITIONS. SUCH METHODS AS CHROMIUM TRIOXIDE IN PYRIDINE,³⁴ CHROMIUM TRIOXIDE IN ACETONE³⁵ AND CHROMIUM TRIOXIDE IN ACETIC ACID³⁶ PRODUCED ONLY DECOMPOSITION PRODUCTS WHEN EITHER OF THE ABOVE CONVERSIONS WAS ATTEMPTED. 6-OXOCRINAMINE IS OXIDIZED TO 6,11-DIOXOCRINAMINE (55) WITH CHROMIUM TRIOXIDE IN DIMETHYLFORMAMIDE³⁷ BUT IN POOR (10 - 20 %) YIELDS. THE BEST REAGENT FOR CARRYING OUT THIS OXIDATION IS ACETIC ANHY-

DRIDE IN DIMETHYLSULFOXIDE.³⁸ YIELDS OF 55 FROM THIS REACTION WERE GENERALLY GREATER THAN 90 %. 6,11-DIOXOCRINAMINE SHOWS CARBONYL ABSORPTION IN THE INFRARED AT 5.72 AND 5.92 μ . THE FORMER ABSORPTION IS SIMILAR TO THAT OBSERVED FOR 11-OXOHAE-MANTHAMINE (5.72 μ)¹⁸ AND THE LATTER ABSORPTION IS CONSISTENT WITH THAT EXPECTED FOR THE LACTAM CARBONYL. THE ULTRAVIOLET SPECTRUM OF 55 WAS COMPLEX WITH ABSORPTION AT 224, 234, 277 AND 326 $m\mu$. BOTH CARBONYL GROUPS ARE REDUCED SIMULTANEOUSLY WITH LITHIUM ALUMINUM TO GIVE TWO PRODUCTS, ONE OF WHICH IS 6-HYDROXYCRINAMINE. SINCE THE REDUCTION OF 6-OXOCRINAMINE GIVES ONLY ONE PRODUCT, THE OTHER PRODUCT FROM THE REDUCTION OF 55 IS PROBABLY 11-EPI-6-HYDROXYCRINAMINE. FURTHER IDENTIFICATION OF THIS COMPOUND WAS NOT MADE. A SIMILAR REDUCTION OF 55 WITH LITHIUM ALUMINUM DEUTERIDE GIVES 6-HYDROXYCRINAMINE-6,11-D₂ (56) AS ONE OF THE PRODUCTS. THE INFRARED SPECTRUM (FIG. 5B) OF 56 SHOWS WEAK C-D STRETCHING BANDS IN THE 4.3 μ REGION.



ACETIC ANHYDRIDE IN DIMETHYLSULFOXIDE CONVERTS 6-HYDROXYCRINAMINE TO 6-ACETYL-11-OXOCRINAMINE (57). UTILIZING OPTIMUM

FIG. 5: INFRARED SPECTRA

A: 6,11-DIOXOCRINAMINE (55)

B: 6-HYDROXYCRINAMINE-6,11-D₂ (56)

C: 6-ACETYL-11-OXOCRINAMINE (57)

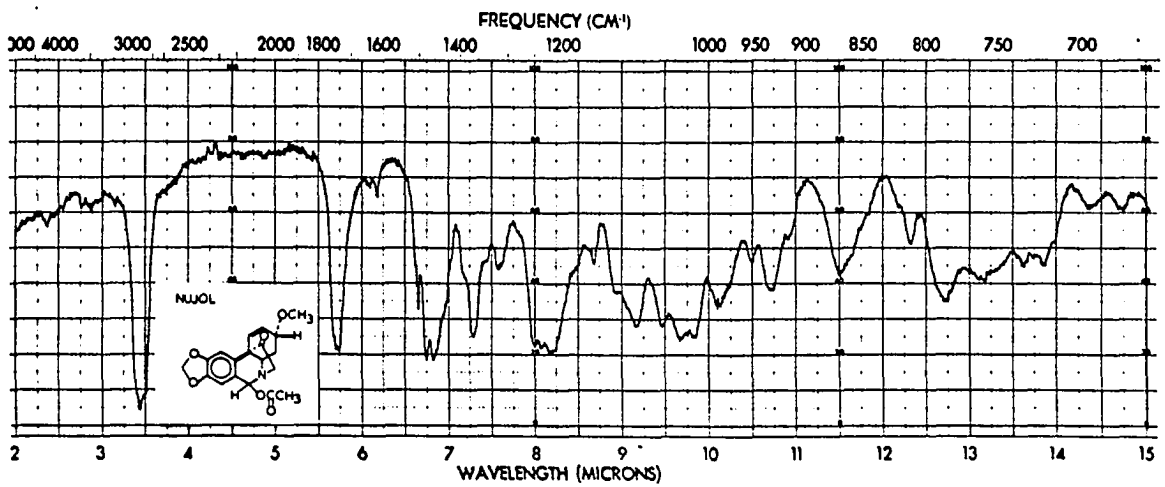
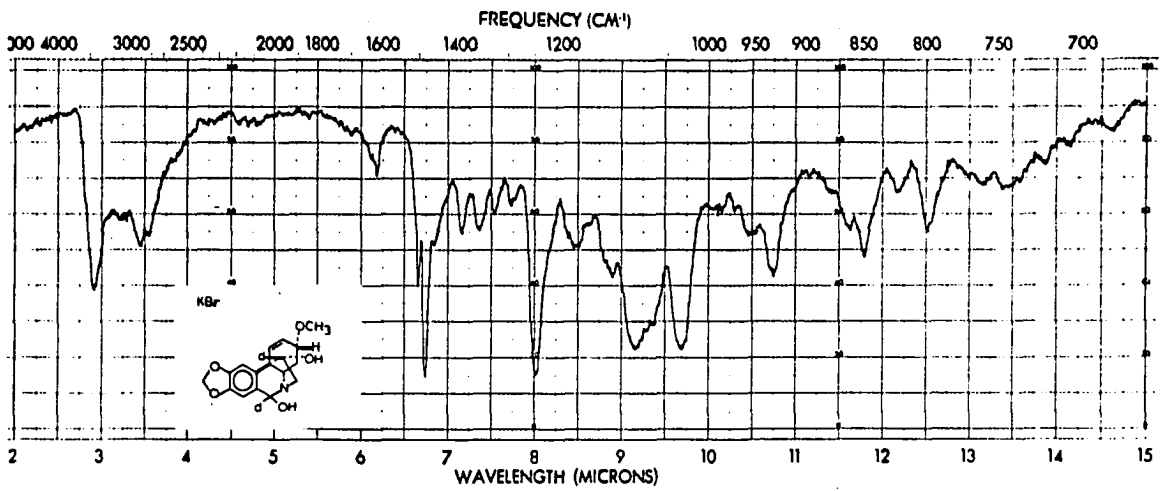
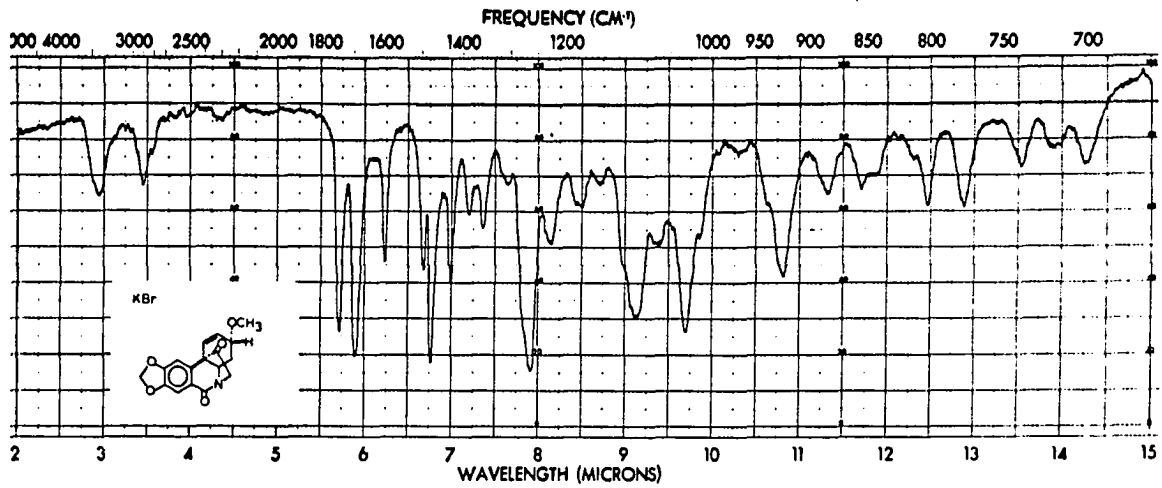
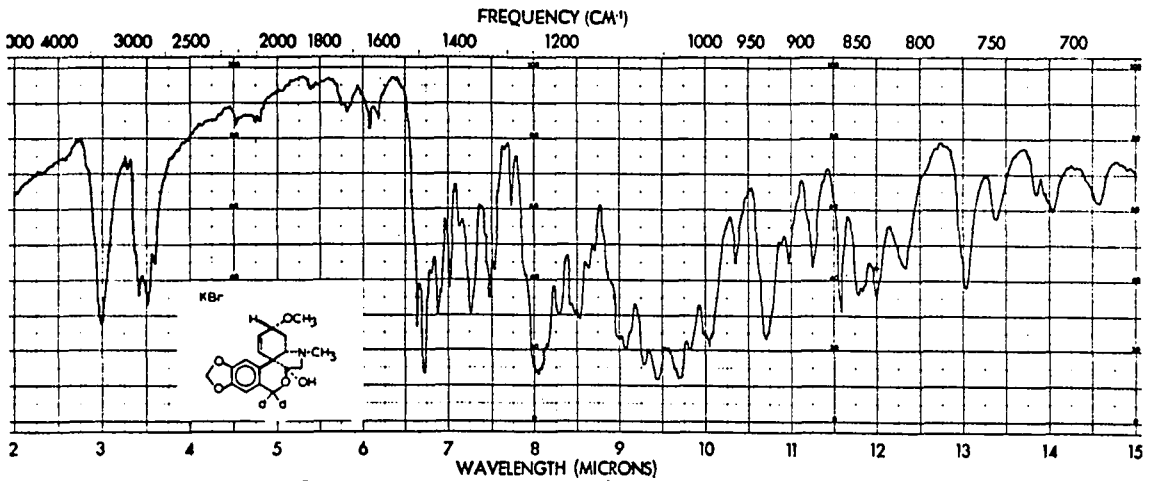
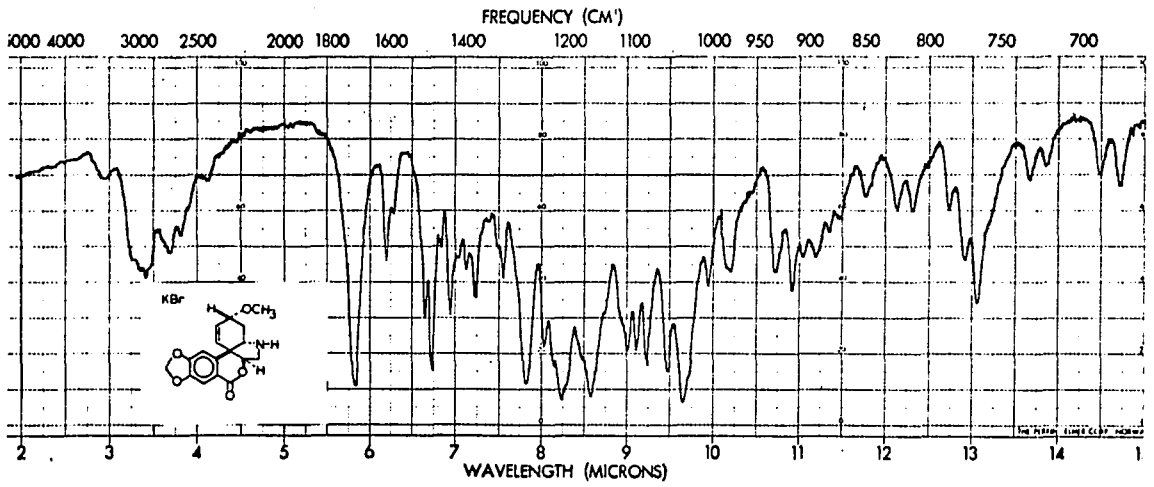
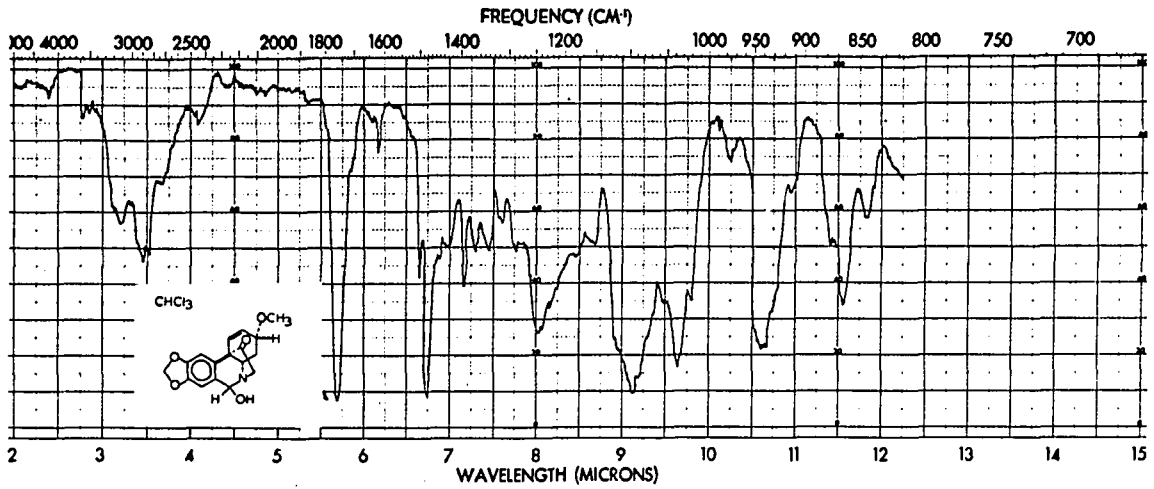


FIG. 6: INFRARED SPECTRA

A: 6-HYDROXY-11-OXOCRINAMINE (58)

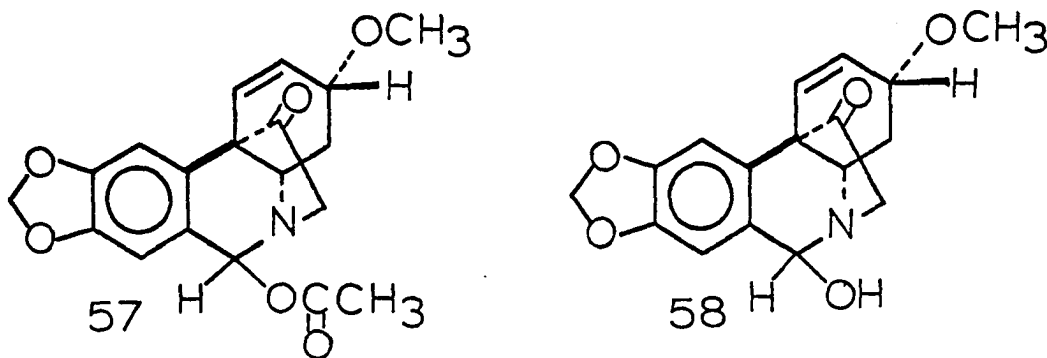
B: 6A-EPI-N-DEMETHYLMACRONINE (82)

C: CRIWELLINE-8-D₂ (94)



RESOLUTION, TWO CARBONYL PEAKS WERE FOUND IN THE INFRARED SPECTRUM OF 57 (FIG. 5C) AT 5.70 AND 5.74 μ . ULTRAVIOLET ABSORPTION OF 57 WAS FOUND AT 251 AND 293 $m\mu$ WITH SHOULDERS AT 311 AND 323 $m\mu$. A SIMILAR ULTRAVIOLET SPECTRUM WAS NOTED FOR 11-OXOHAEMANTHAMINE.¹⁸ 6-ACETYL-11-OXOCRINAMINE IS REDUCED WITH LITHIUM ALUMINUM HYDRIDE TO 6-HYDROXYCRINAMINE AND APPARENTLY 11-EPI-6-HYDROXYCRINAMINE.

THE ACETYL GROUP OF 57 CAN BE REMOVED BY METHANOLYSIS TO GIVE 6-HYDROXY-11-OXOCRINAMINE (58). THE INFRARED SPECTRUM OF 58 EXHIBITED STRONG CARBONYL ABSORPTION AT 5.69 μ (FIG. 6A). 6-HYDROXY-11-OXOCRINAMINE ABSORBS IN THE ULTRAVIOLET AT 246 AND 293 $m\mu$ WITH SHOULDERS AT 312 AND 323 $m\mu$.



DISCUSSION OF THE NUCLEAR MAGNETIC RESONANCE SPECTRA

THE NUCLEAR MAGNETIC RESONANCE SPECTRA DESCRIBED IN THIS THESIS WERE OBTAINED ON EITHER A VARIAN HR-60 OR A-60 SPECTROMETER. CHEMICAL SHIFTS ARE EXPRESSED IN PARTS PER MILLION (P.P.M.) DOWNFIELD FROM AN INTERNAL TETRAMETHYLSILANE (TMS) STANDARD. IN MANY CASES OVERLAPPING PEAKS HAVE MADE ASSIGN-

MENT UNCERTAIN AND FIELD SWEEP SPIN DECOUPLING EXPERIMENTS³⁹ WERE PERFORMED AS NEEDED.

IT SEEMED LIKELY THAT THE SPURIOUS PEAKS IN THE N.M.R. SPECTRA OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE WERE IN SOME WAY RELATED TO THE SUBSTITUTION OF A HYDROXYL GROUP AT C-6 BECAUSE CRINAMINE AND HAEMANTHAMINE HAVE NORMAL SPECTRA.³⁰ SINCE THE C-6 HYDROXYL GROUP PROBABLY CAUSES THE PECULIARITIES OBSERVED, THE N.M.R. SPECTRA OF THE ACETYL DERIVATIVES WERE OBTAINED.

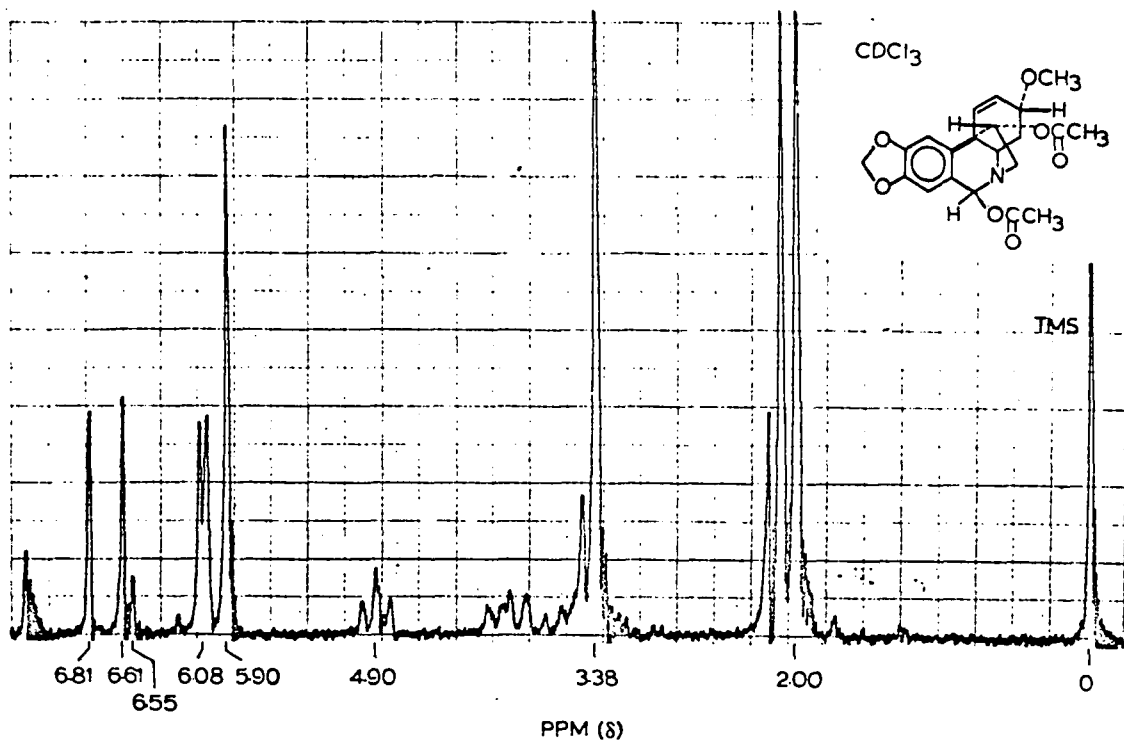
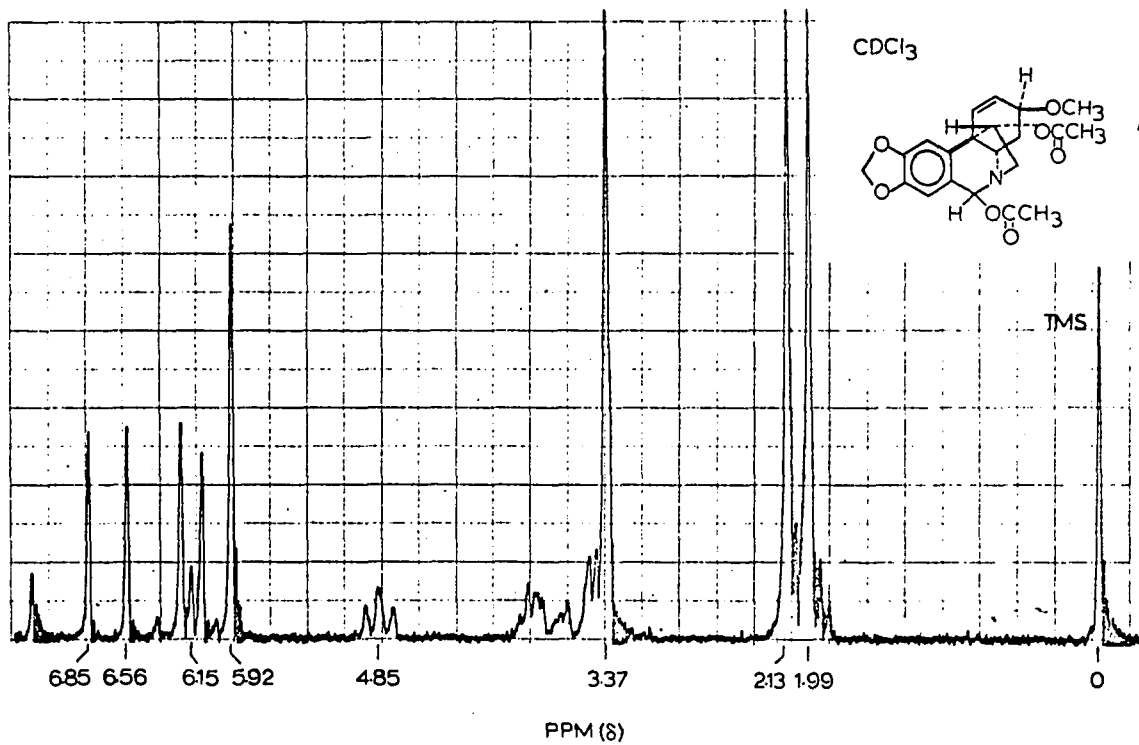
THE N.M.R. SPECTRA OF 6,11-DIACETYLHAEMANTHIDINE (43) AND 6,11-DIACETYL-6-HYDROXYCRINAMINE (42) ARE SHOWN IN FIGS. 7A AND 7B, RESPECTIVELY. THE TWO SINGLETs IN THE SPECTRUM OF 42 AT 6.81 AND 6.61 P.P.M. ARE TENTATIVELY ASSIGNED TO THE AROMATIC PROTON RESONANCES. THE PEAKS AT 6.08 P.P.M. MUST BE ASSIGNED TO THE OLEFINIC PROTON RESONANCES AND THE SINGLET AT 5.90 P.P.M. IS PRODUCED BY THE METHYLENEDIOXY PROTONS. THE ROUGH TRIPLET AT 4.90 P.P.M. IS ASSIGNED TO THE PROTON AT C-11. THE REMAINING ASSIGNABLE PEAKS ARE THE THREE PROTON SINGLETs AT 3.38 P.P.M. (METHOXYL) AND 2.00 P.P.M. (ACETYL). AN EXAMINATION OF THE INTEGRAL OF THE SPECTRUM REVEALS THAT THE C-6 PROTON RESONANCE IS SUPERIMPOSED UPON THE OLEFINIC PROTON PEAKS AT 6.08 P.P.M.

THE N.M.R. SPECTRUM OF 43 IS SIMILAR TO THAT OF 42. AGAIN THE INTEGRAL INDICATED THAT THE C-6 PROTON RESONANCE IS SUPERIMPOSED UPON THE OLEFINIC PROTON RESONANCES AT 6.15 P.P.M. A CLOSER STUDY OF THE N.M.R. SPECTRA OF 42 AND 43 REVEALS

FIG. 7: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6,11-DIACETYL-6-HYDROXYCRINAMINE (42)

B: 6,11-DIACETYLHAEMANTHIDINE (43)



TWO SMALL UNASSIGNED PEAKS AT 6.15 P.P.M. (FIG. 7A) AND 6.55 P.P.M. (FIG. 7B), WHICH SUGGEST THAT IRREGULARITIES EXIST IN THESE SPECTRA ALSO.

THE N.M.R. SPECTRUM OF DIHYDRO-6-HYDROXYCRINAMINE IS SHOWN IN FIG. 8A. THE AROMATIC PROTONS APPEAR AS A NEAR SINGLET AT 6.68 P.P.M. WITH ANOTHER SMALL PEAK AT 6.76 P.P.M. THE METHYLENEDIOXY PROTONS GIVE RISE TO A SINGLET AT 5.96 P.P.M. AND THE TWO NONINTEGRAL PEAKS APPEAR AT 5.33 AND 4.78 P.P.M. THE SINGLET AT 3.26 P.P.M. IS ASSIGNED TO THE METHOXYL PROTON RESONANCES. TWO BROAD PEAKS WERE REMOVED FROM THE 5.9 AND 5.3 P.P.M. REGIONS WHEN THE SAMPLE WAS SHAKEN WITH DEUTERIUM OXIDE (FIG. 8B). THE INTEGRALS OF THE SMALL PEAKS AT 6.76 AND 5.33 P.P.M. ARE NEARLY EQUAL. FROM THIS DATA IT IS EVIDENT THAT THE DOUBLE BOND IN RING C HAS LITTLE OR NO EFFECT UPON THE PHENOMENA BEING OBSERVED.

TO ELIMINATE THE PROBLEM OF SUPERIMPOSITION OF PEAKS IN THE SPECTRA OF THE DIACETATES, THE DIACETYLDIHYDRO DERIVATIVES WERE SYNTHESIZED. THE AROMATIC PROTONS GIVE RISE TO PEAKS IN THE 6.5 - 6.9 P.P.M. REGION OF THE SPECTRUM OF 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46) AS SHOWN IN FIG. 9A, BUT NOT THE TWO SINGLETs EXPECTED. THE METHYLENEDIOXY PROTONS PRODUCE A SINGLET AT 5.93 P.P.M. AND THE C-11 PROTON GIVES A TRIPLET AT 4.94 P.P.M. THE METHOXYL PROTONS PRODUCE A SINGLET AT 3.42 P.P.M. AND THE ACETOXYL PROTONS APPARENTLY GIVE RISE TO THREE SINGLETs IN THE 2.1 P.P.M. REGION. THE BENZYLIC PROTON PRODUCES A SINGLET AT 6.10 P.P.M. HOWEVER THE INTEGRAL SHOWS THAT

FIG. 8: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: DIHYDRO-6-HYDROXYCRINAMINE (40)
B: 40 + DEUTERIUM OXIDE

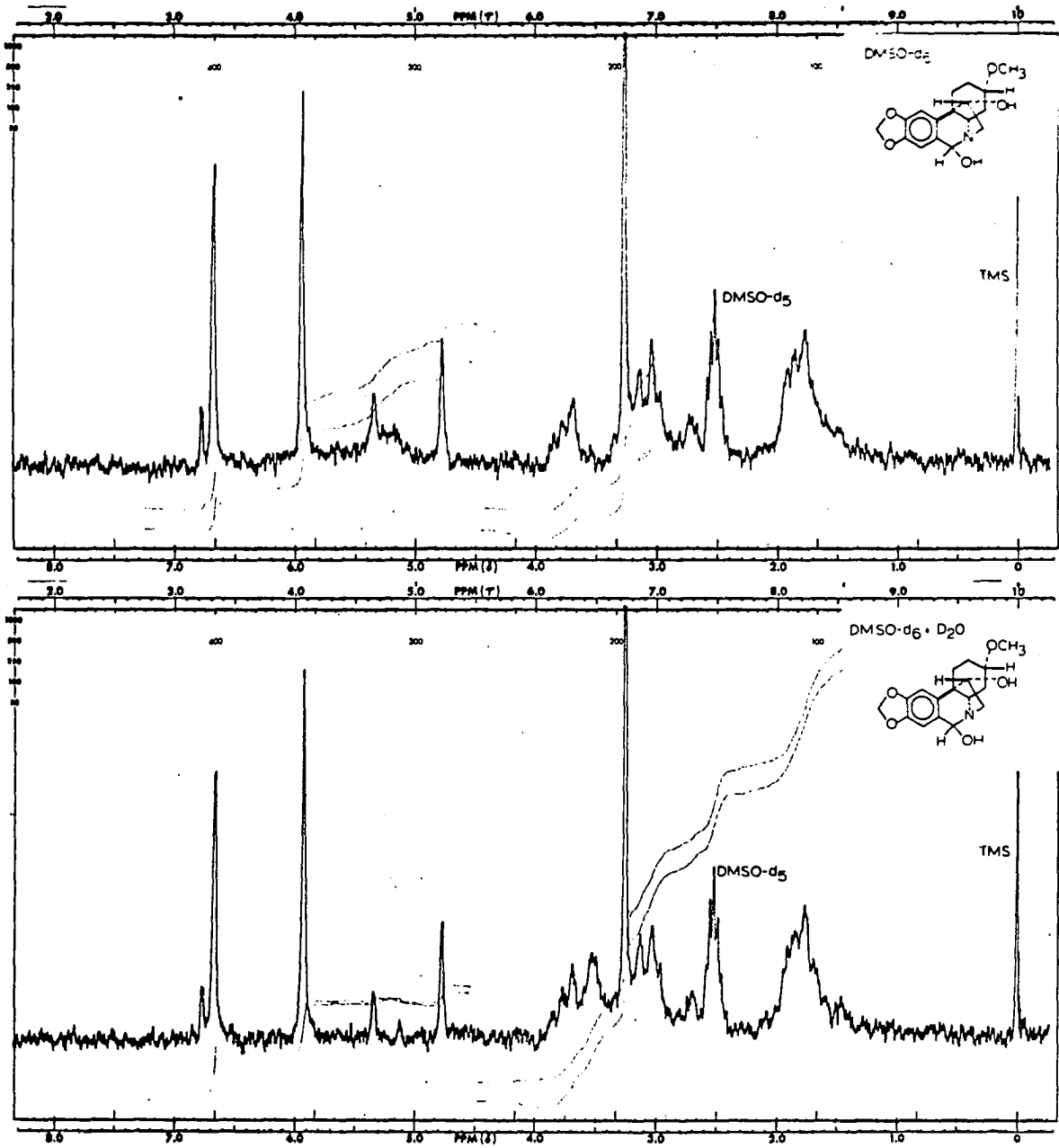
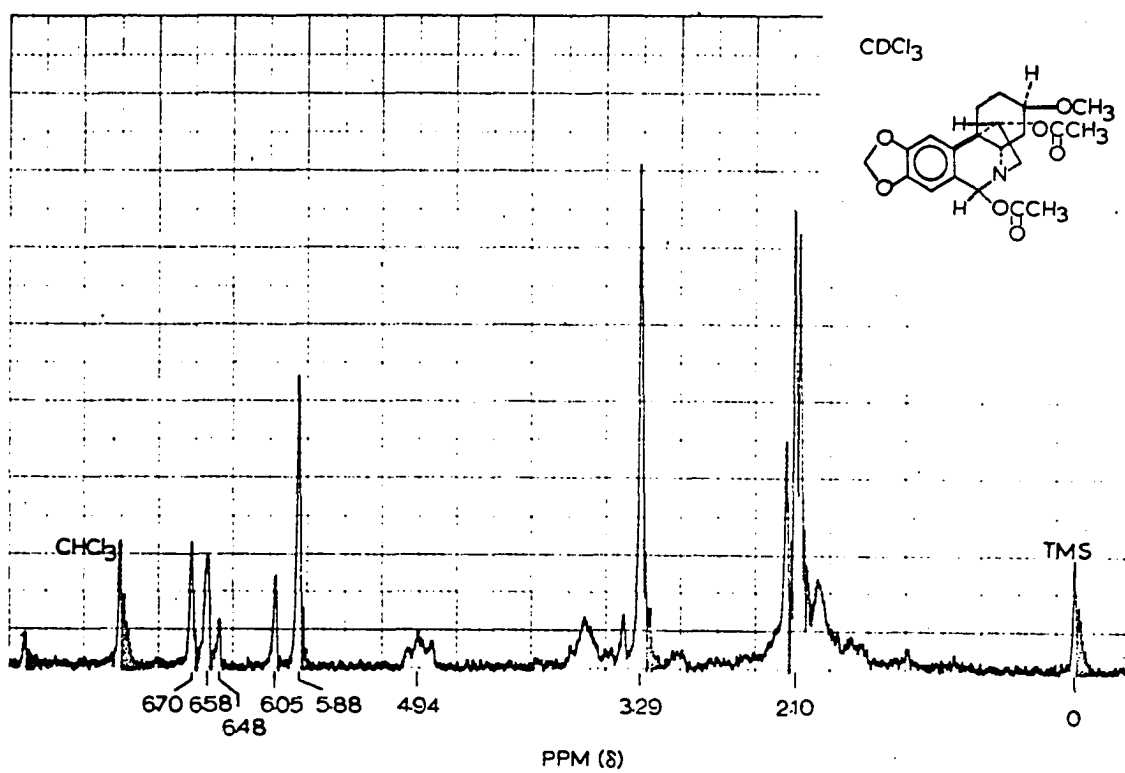
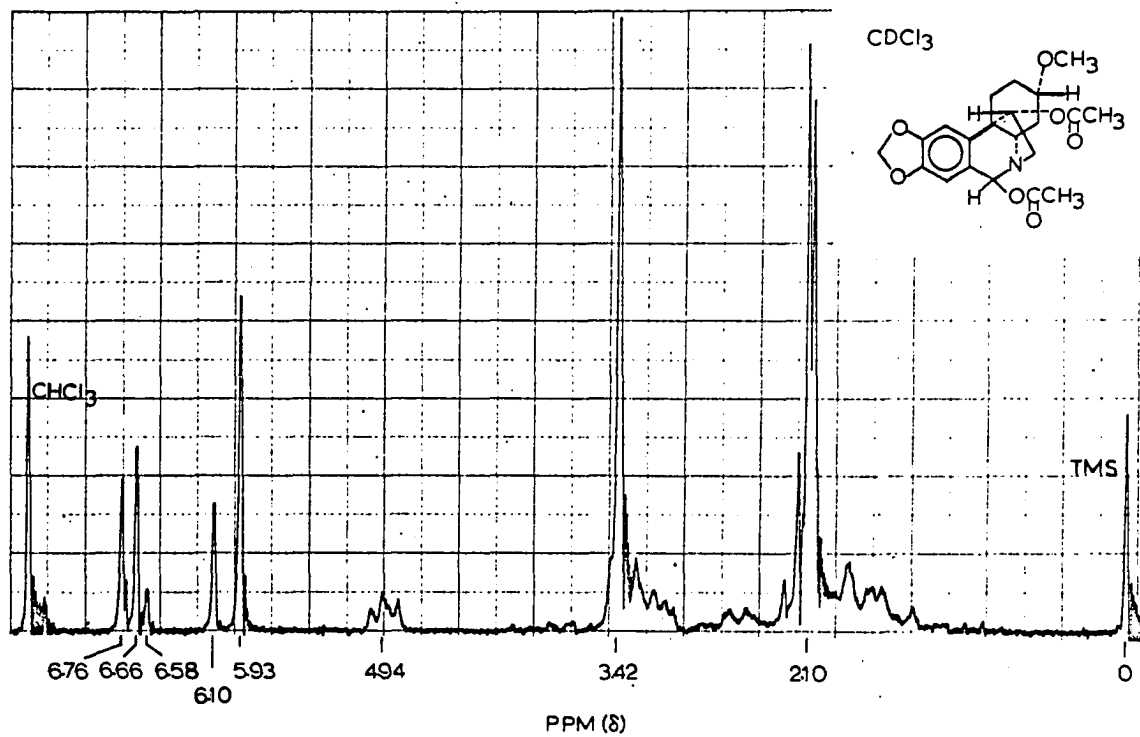


FIG. 9: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46)

B: 6,11-DIACETYLDIHYDROHAEMANTHIDINE (47)



ITS AREA DOES DOES NOT CORRESPOND TO THAT OF ONE PROTON. THE AREA OF THE AROMATIC PROTON PEAKS INTEGRATES FOR MORE THAN TWO PROTONS. THE N.M.R. SPECTRUM OF 47 (FIG. 9B) CAN BE INTERPRETED SIMILARLY.

SPIN DECOUPLING EXPERIMENTS WERE CARRIED OUT BY IRRADIATING EITHER THE SMALL PEAK AT 6.58 P.P.M. OR THE LARGER PEAK AT 6.10 P.P.M. AND SCANNING THE AROMATIC PROTON REGION IN THE SPECTRUM OF 46. IRRADIATION OF THE PEAK AT 6.10 P.P.M. PRODUCED A MARKED SHARPENING IN THE PEAK AT 6.66 P.P.M. IRRADIATION OF THE PEAK AT 6.58 P.P.M. PRODUCED A SIMILAR SHARPENING IN THE PEAK AT 6.76 P.P.M. THESE EXPERIMENTS LED TO THE CONCLUSION THAT ACETYLATION CAUSED A SHIFT OF THE PEAKS AT 5.00 AND 5.58 P.P.M. IN THE SPECTRUM OF 6-HYDROXYCRINAMINE TO 6.10 AND 6.66 OR 6.76 P.P.M., RESPECTIVELY, IN THE SPECTRUM OF 46. A DEFINITE ASSIGNMENT CANNOT BE GIVEN TO THE PEAKS AT 6.66 AND 6.76 P.P.M. BECAUSE IT HAS NOT BEEN DETERMINED WHICH PEAK IS A C-6 PROTON RESONANCE AND WHICH PEAK IS A C-7 PROTON RESONANCE.

A METHOD TO DETERMINE WHICH PEAK BELONGS TO WHICH PROTON WAS FOUND BY THE ADDITION OF TRIFLUOROACETIC ACID TO THE SAMPLE OF 46. PROTONATION OF THE ELECTRONEGATIVE ATOMS WOULD BE EXPECTED AND THE DESHIELDING EFFECT OF THIS PROTONATION IS APPARENT IN THE N.M.R. SPECTRUM.⁴⁰ THE CHEMICAL SHIFTS OF ALL PROTONS BONDED TO A CARBON BEARING AN ELECTRONEGATIVE ATOM ARE SHIFTED DOWNFIELD BY VARYING DEGREES. THE LARGEST SHIFTS OCCUR WHEN THE ELECTRONEGATIVE ATOM IS AN AMINO NITROGEN.⁴⁰ THIS SHIFT CAN BE USED TO AN ADVANTAGE IN ASSIGNING PEAKS IN

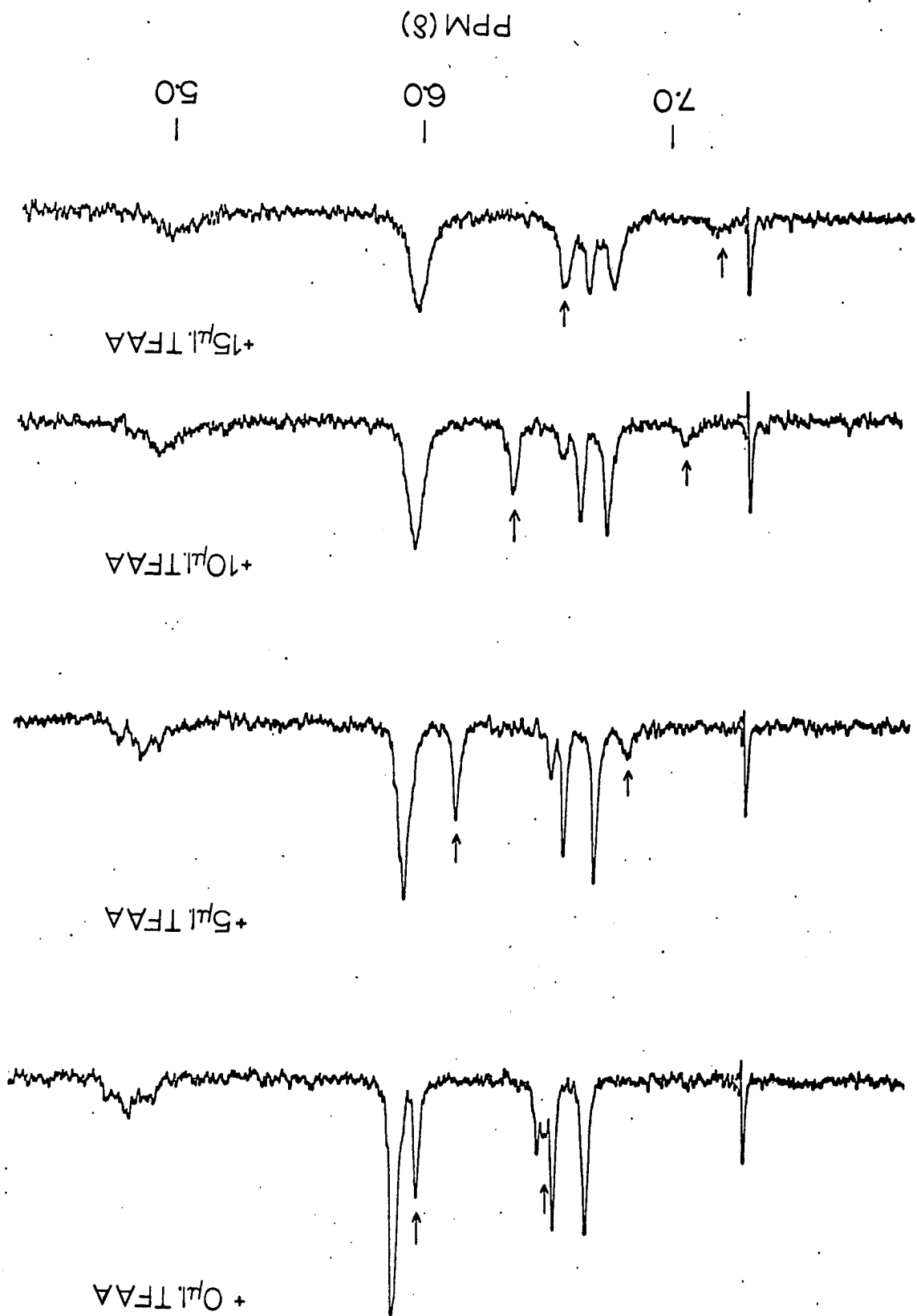
FIG. 10: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46)

B: 46 + 5 μ L. OF TFAA

C: 46 + 10 μ L. OF TFAA

D: 46 + 15 μ L. OF TFAA

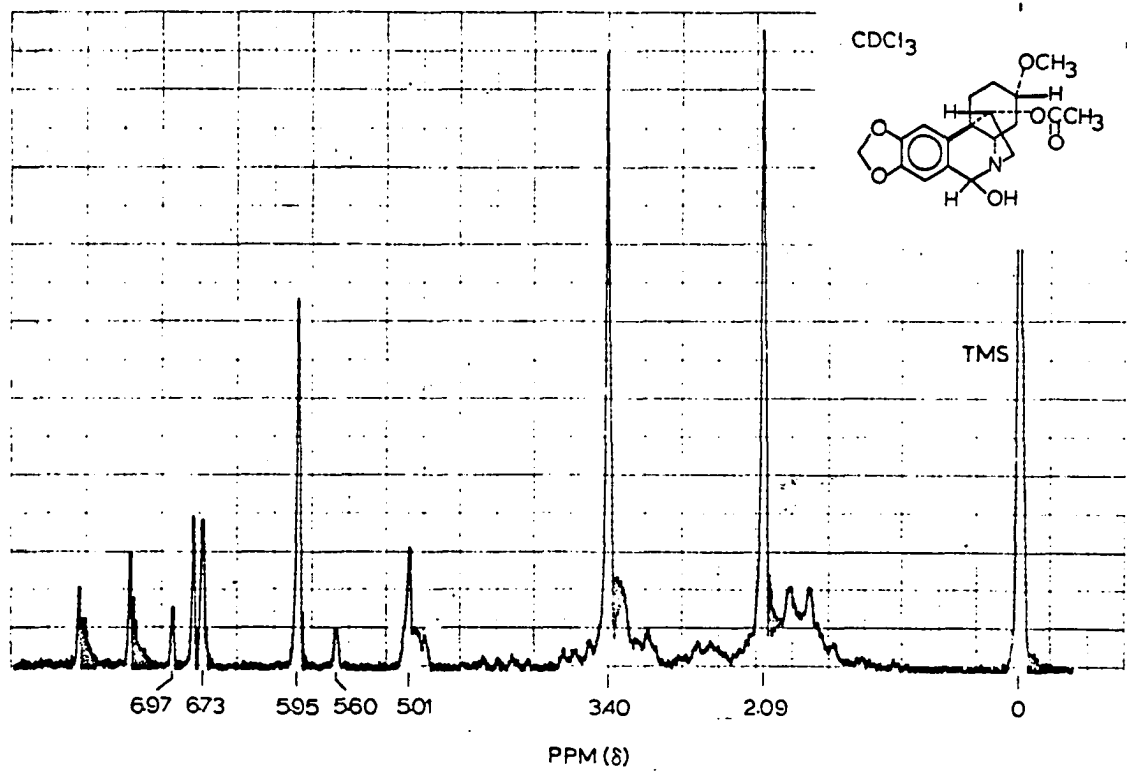
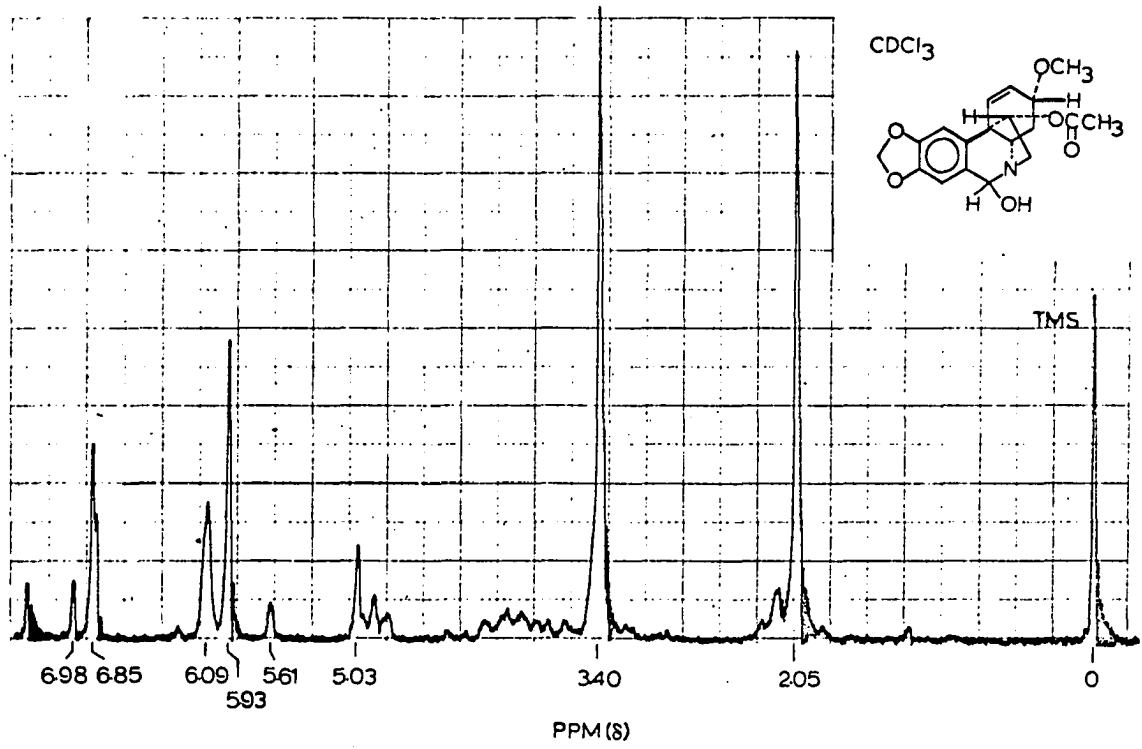


A NONPROTONATING SOLVENT SUCH AS DEUTERIOCHLOROFORM OR CARBON TETRACHLORIDE. THE LOW FIELD REGION OF THE N.M.R. SPECTRUM OF 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE IN CARBON TETRACHLORIDE IS SHOWN IN FIG. 10A. THE ADDITION OF 5 μ L. ALIQUOTS OF TRIFLUOROACETIC ACID PRODUCED SUBSEQUENT CHANGES IN THE SPECTRUM AS SHOWN IN FIGS. 10B, 10C AND 10D. IT IS APPARENT THAT THE PEAKS ORIGINALLY AT 6.03 AND 6.54 P.P.M. MOVE DOWNFIELD WITH SUBSEQUENT ADDITIONS OF TRIFLUOROACETIC ACID. THESE DATA SUGGESTS THAT THESE TWO PEAKS (AT 6.03 AND 6.54 P.P.M.) ARE PRODUCED BY THE BENZYLIC PROTON AND THAT THE 6-ACETYL DERIVATIVES MAY BE MIXTURES OF TWO COMPONENTS.

THE N.M.R. SPECTRUM OF 11-ACETYL-6-HYDROXYCRINAMINE (44) HAS SEVERAL PEAKS IN THE 6.6 - 7.0 P.P.M. REGION (FIG. 11A). ALL OF THESE PEAKS ARE ASSIGNED TO THE AROMATIC PROTONS BECAUSE THE ENTIRE AREA OF THESE PEAKS INTEGRATED FOR TWO PROTONS. THE OLEFINIC PROTONS GIVE RISE TO PEAKS CENTERED AT 6.09 P.P.M. AND THE METHYLENEDIOXY PROTONS PRODUCE A SINGLET AT 5.93 P.P.M. THE 4 - 6 P.P.M. REGION OF THE SPECTRUM IS ALMOST A COMBINATION OF THE SPECTRA OF 6-HYDROXYCRINAMINE AND 6,11-DIACETYL-6-HYDROXYCRINAMINE. THIS SIMILARITY LEADS TO THE ASSIGNMENT OF THE PEAKS AT 5.03 AND 5.61 P.P.M. AS THE C-6 PROTON AND THE TRIPLET AT 5.0 P.P.M. AS THE C-11 PROTON. THE SINGLET AT 3.40 P.P.M. IS THE METHOXYL PROTON RESONANCES AND THE ACETOXYL PROTONS PRODUCE THE SINGLET AT 2.05 P.P.M.

THE N.M.R. SPECTRUM OF 11-ACETYLDIHYDRO-6-HYDROXYCRINAMINE (48) IS SIMILAR TO THAT OF 44. THE AROMATIC PROTONS

FIG. 11: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: 11-ACETYL-6-HYDROXYCRINAMINE (44)
B: 11-ACETYLDIHYDRO-6-HYDROXYCRINAMINE (48)



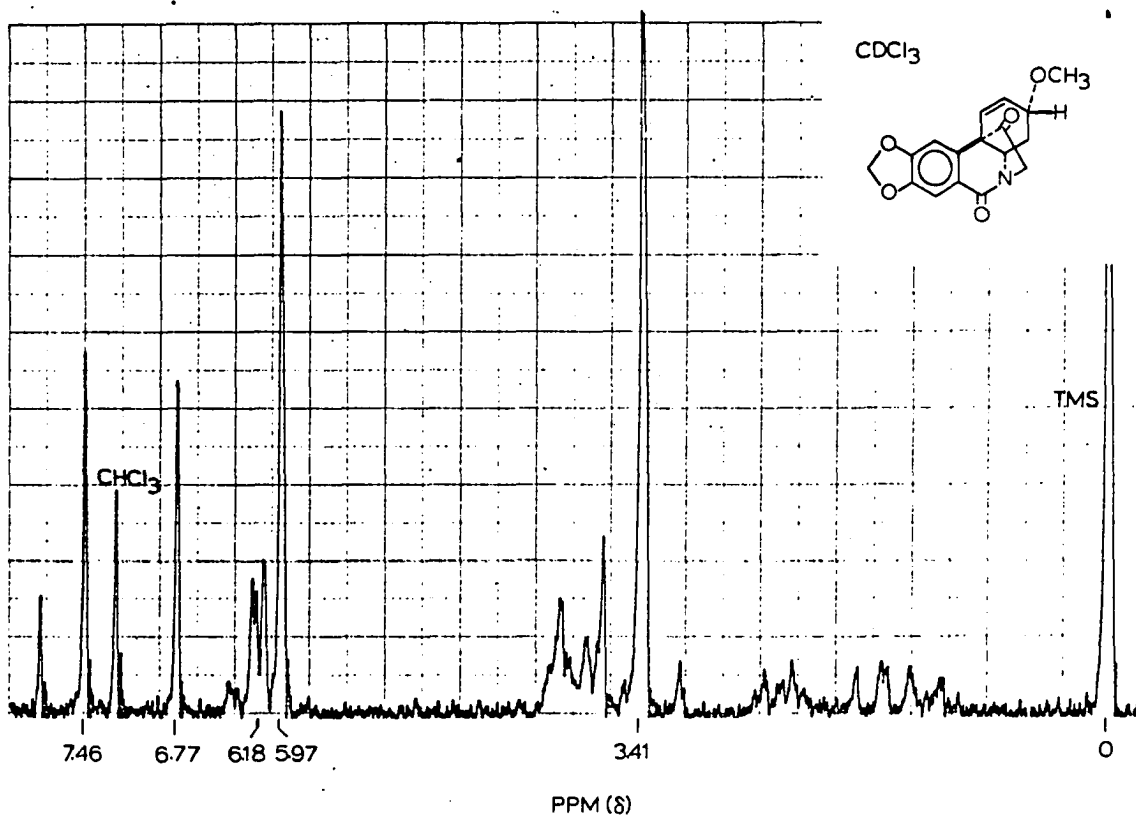
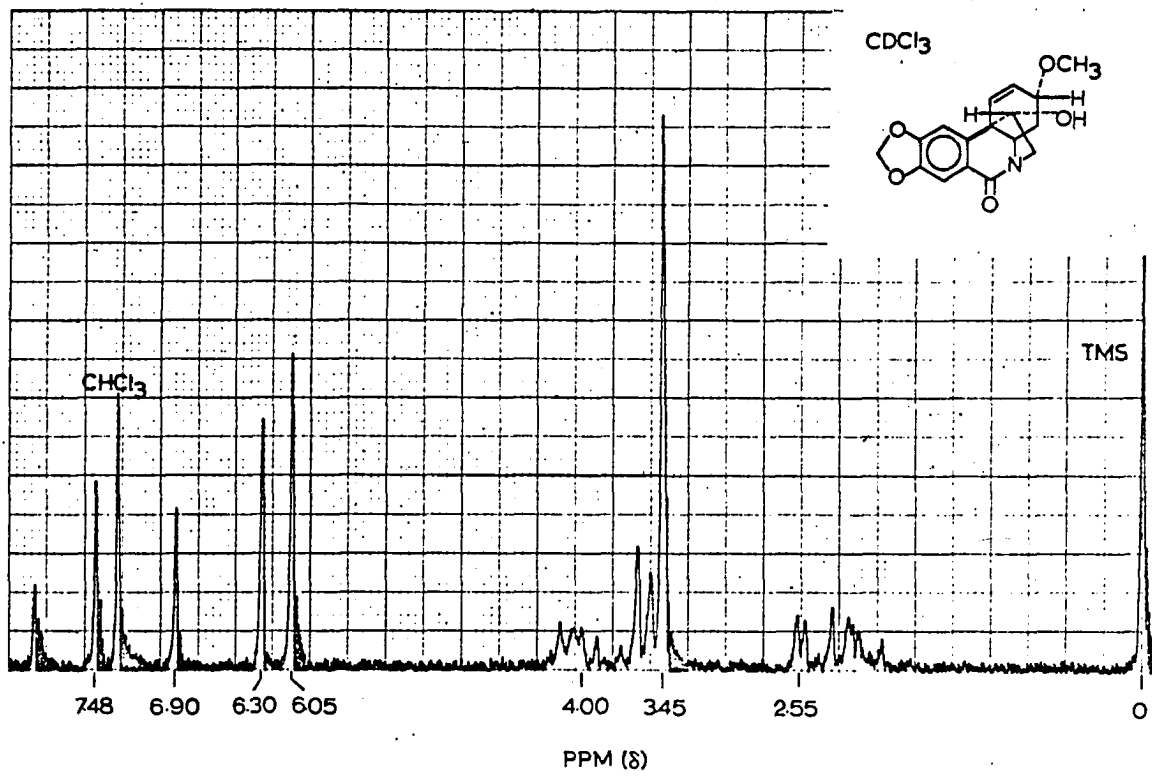
GIVE RISE TO SEVERAL PEAKS IN THE 6.7 - 7.0 P.P.M. REGION (FIG. 11B). THE BENZYLIC PROTON PRODUCES PEAKS AT 5.01 AND 5.61 P.P.M. WITH THE FORMER PEAK SUPERIMPOSED UPON THE TRIPLET PRODUCED BY THE C-11 PROTON. THE METHOXYL AND ACETOXYL PROTON SINGLET APPEAR AT 3.40 AND 2.09 P.P.M., RESPECTIVELY.

THE PROTON AT THE 10 POSITION OF 6-OXOCRINAMINE (37) PRODUCES A SINGLET AT 6.90 P.P.M. (FIG. 12A) AND THE C-7 PROTON RESONANCE APPEARS AT 7.48 P.P.M. THIS ASSIGNMENT IS BASED UPON THE FACT THAT PROTONS ORTHO TO UNSATURATED GROUPS ARE SHIFTED DOWNFIELD.^{41, p. 62} THE OLEFINIC PROTONS GIVE RISE TO A SHARP SINGLET AT 6.30 P.P.M. AND THE METHYLENEDIOXY PROTONS GIVE A SINGLET AT 6.05 P.P.M. THE COMPLEX MULTIPLY AT 4.00 P.P.M. IS ASSIGNED TO THE C-3 PROTON. THE METHOXYL PROTONS PRODUCE A SINGLET AT 3.45 P.P.M. WHICH IS APPARENTLY SUPERIMPOSED UPON THE PEAKS PRODUCED BY PEAKS AT POSITIONS 4A, 11 AND 12. THE DOUBLET AT 2.55 P.P.M. IS ASSIGNED TO THE HYDROXYL PROTON BECAUSE BOTH PEAKS WERE REMOVED WHEN THE SAMPLE WAS SHAKEN WITH DEUTERIUM OXIDE. THE FACT THAT THE HYDROXYL PROTON APPEARS HERE AS A DOUBLET IS UNUSUAL AND BEARS COMMENT. COUPLING BETWEEN A HYDROXYL PROTON AND PROTONS ON THE HYDROXYL BEARING CARBON IS SELDOM OBSERVED IN NONHYDROGEN BONDING SOLVENTS SUCH AS DEUTERIOCHLOROFORM OR CARBON TETRACHLORIDE BECAUSE OF THE RAPID INTERMOLECULAR HYDROGEN EXCHANGE CATALYZED BY ACID IMPURITIES IN THE SOLVENT.^{41, p. 28} COUPLING IS MOST PROBABLY OBSERVED IN THIS CASE BECAUSE THE HYDROXYL GROUP IS STRONGLY HYDROGEN BONDED TO THE DOUBLE BOND IN RING C WHICH

FIG. 12: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6-OXOCRINAMINE (37)

B: 6,11-DIOXOCRINAMINE (55)



REDUCES INTERMOLECULAR EXCHANGE TO A MINIMUM. TWO INTERESTING COUNTERACTING EFFECTS ARE PRESENT WHEN HYDROGEN BONDING TO A DOUBLE BOND OCCURS. HYDROGEN BONDING USUALLY PRODUCES A DOWN-FIELD SHIFT DUE TO THE DECREASE IN ELECTRON DENSITY AROUND THE PROTON.^{42, p. 409} HOWEVER, IN ORDER TO BE STRONGLY HYDROGEN BONDED TO A DOUBLE BOND THE PROTON MUST ALSO BE IN THE SHIELDING AREA OF THE DOUBLE BOND.^{41, p. 124} THIS EFFECT PRODUCES AN UPFIELD SHIFT BECAUSE OF AN INCREASE IN ELECTRON DENSITY IN THE AREA OF THE PROTON. AS A RESULT, THE TWO EFFECTS ARE CANCELLING.

THE INTRAMOLECULAR HYDROGEN BONDING CAN ALSO BE STUDIED BY HIGH DILUTION INFRARED METHODS.⁴³ THE TWO HYDROXYL GROUPS OF HAEMANTHIDINE AND 6-HYDROXYCRINAMINE ABSORB AT NEARLY THE SAME FREQUENCY (3595 cm^{-1}). UPON HYDROGENATION, A SECOND BAND APPEARS AT 3635 cm^{-1} WHICH INDICATES A FREE HYDROXYL ABSORPTION. THE INTRAMOLECULAR HYDROGEN BONDING IN 6-OXOCRINAMINE IS WEAKER THAN IN THE PARENT ALKALOID. THIS FACT IS PROBABLY DUE TO THE GREATER DISTANCE BETWEEN THE HYDROXYL GROUP AND THE DOUBLE BOND PRODUCED BY THE INTRODUCTION OF THE TRIGONAL CARBON AT C-6. THE INFRARED HYDROGEN BONDING STUDIES ARE SUMMARIZED IN TABLE I. 11-ACETYL-6-HYDROXYCRINAMINE PROVIDES A MEASURE OF THE C-6 HYDROXYL STRETCHING FREQUENCY.

THE ABSENCE OF PEAKS AT 5.58 AND 5.00 P.P.M. IN THE N.M.R. SPECTRUM OF 6-OXOCRINAMINE SUGGESTS THAT THEIR OCCURRENCE IS SOLELY DEPENDENT UPON HYDROXYL SUBSTITUTION AT C-6. 6-OXOCRINAMINE IS REDUCED TO 6-HYDROXYCRINAMINE WITH EITHER LITHIUM

TABLE 1: HYDROGEN BONDING IN 6-HYDROXYCRINAMINE, HAEMANTHIDINE AND THEIR DERIVATIVES

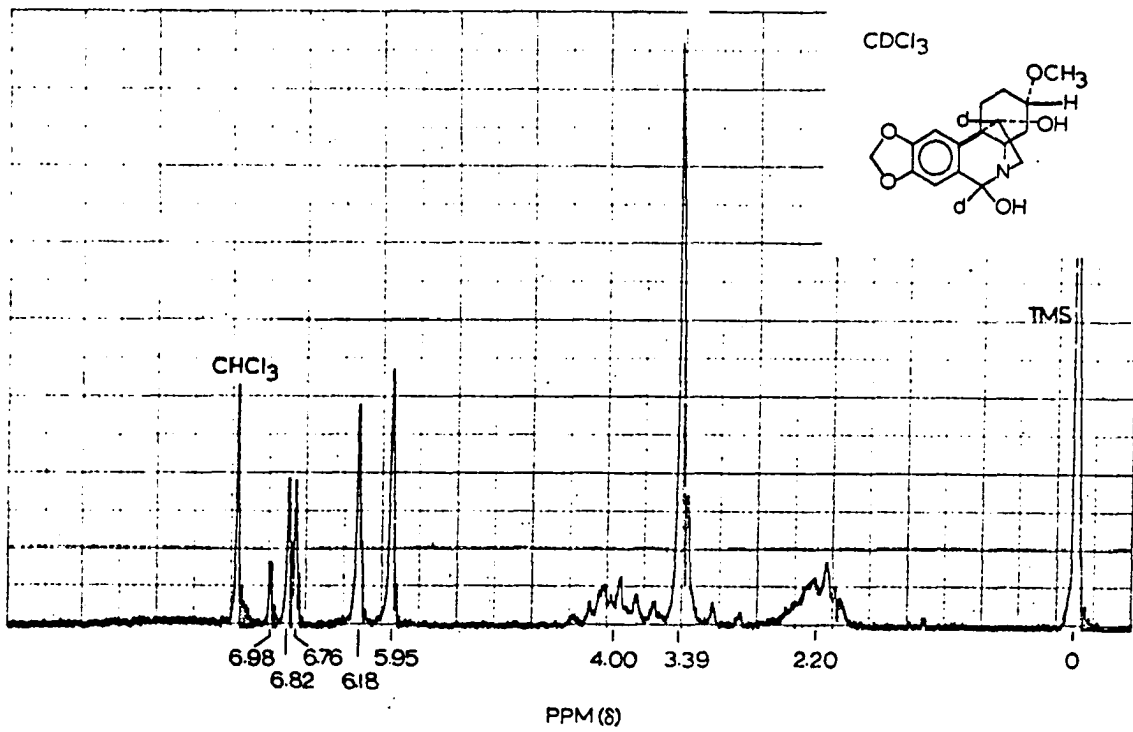
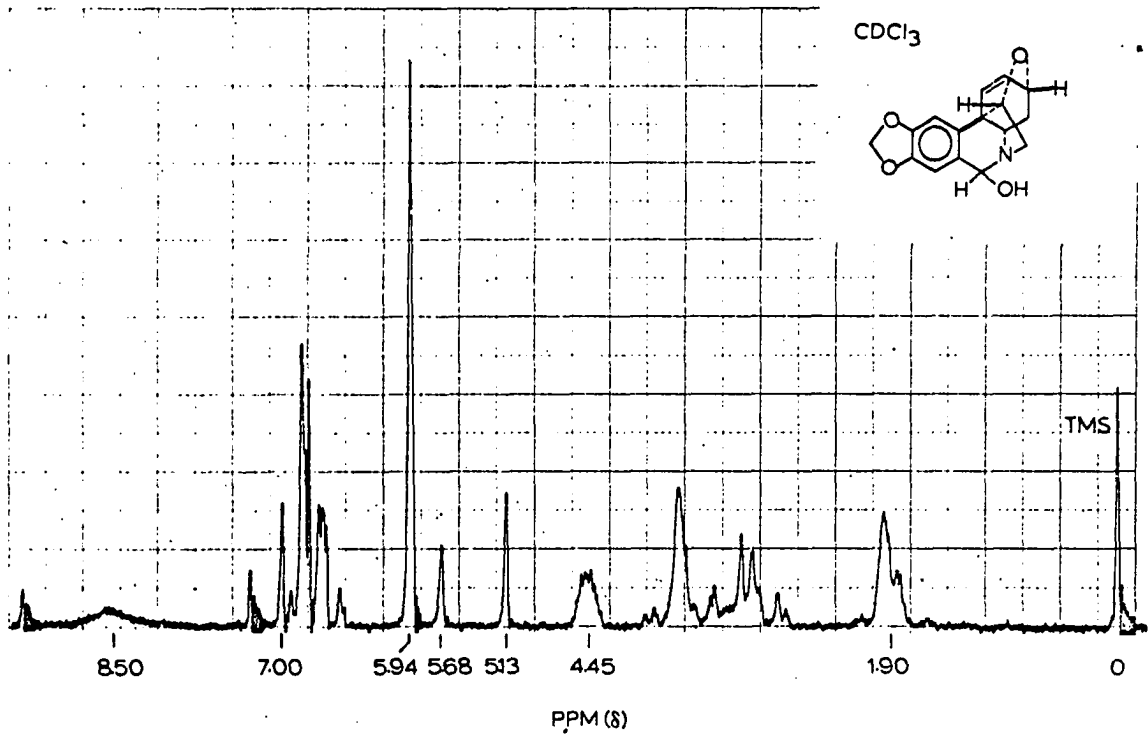
COMPOUND	HYDROXYL STRETCHING FREQUENCY (CM ⁻¹)
HAEMANTHIDINE	3597.5
DIHYDROHAEMANTHIDINE	3595
	3637.5
6-HYDROXYCRINAMINE	3593
DIHYDRO-6-HYDROXYCRINAMINE	3593
	3632
6-OXOCRINAMINE	3602
11-ACETYL-6-HYDROXYCRINAMINE	3593
BENZYL ALCOHOL	3600

ALUMINUM HYDRIDE OR SODIUM BOROHYDRIDE. THE N.M.R. SPECTRUM OF EITHER THE CRUDE, NONCRYSTALLINE PRODUCT OR THE CRYSTALLINE COMPOUND IS IDENTICAL TO THAT OF THE NATURAL ALKALOID. THESE RESULTS PROVE THAT THE PEAKS IN QUESTION ARE NOT IMPURITIES BUT A RESULT OF SOME UNUSUAL FEATURE OF THE ALKALOIDS.

THE N.M.R. SPECTRUM OF 6,11-DIOXOCRINAMINE (55) ALSO DOES NOT EXHIBIT ABNORMALITIES (FIG. 12B). THE SINGLET PEAKS AT 7.46 AND 6.77 P.P.M. ARE ASSIGNED TO THE AROMATIC PROTONS AT C-7 AND C-10, RESPECTIVELY. THE OLEFINIC PROTONS PRODUCE A MULTIPLY AT 6.18 P.P.M. AND THE METHYLENEDIOXY PROTONS GIVE RISE TO A SINGLET AT 5.97 P.P.M. THE SINGLET AT 3.41 P.P.M. IS ASSIGNED TO THE METHOXYL PROTONS BUT THE REMAINING PEAKS IN THE SPECTRUM CANNOT BE ASSIGNED WITHOUT FURTHER INVESTIGATION.

THE N.M.R. SPECTRUM OF APOHAEMANTHIDINE (22) PRESENTS A FORMIDABLE ARRAY OF PEAKS (FIG. 13A), ESPECIALLY IN THE AROMATIC PROTON REGION. DEFINITE ASSIGNMENTS MAY BE GIVEN TO THE

FIG. 13: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: APOHAEMANTHIDINE (22)
B: 6-HYDROXYCRINAMINE-6,11-D₂ (56)



PEAK AT 5.94 P.P.M. (METHYLENEDIOXY PROTONS) AND THE MULTIPLET AT 1.90 P.P.M. (C-4 PROTONS). SPIN DECOUPLING WAS UTILIZED TO CLARIFY THE ASSIGNMENT OF THE LOW FIELD PEAKS. IRRADIATION OF THE PEAK AT 4.45 P.P.M. SIMPLIFIED THE OLEFINIC PROTONS TO AN AB PATTERN (FIG. 14c). THIS ESTABLISHES THE PEAK AT 4.45 P.P.M. AS THE C-3 PROTON AND AS THE X PART OF AN ABX PATTERN. IRRADIATION OF THE PEAK AT 4.45 P.P.M. HAD LITTLE EFFECT UPON THE PEAK D (SEE FIG. 14c) WHICH INDICATED THIS TO BE LARGELY AN AROMATIC PROTON RESONANCE. IRRADIATION OF THE PEAK AT 5.13 P.P.M. CAUSED THE PEAK B TO SHARPEN WHEREAS IRRADIATION OF THE PEAK AT 5.68 P.P.M. HAD A SIMILAR EFFECT ON PEAK A. PEAKS C AND D WERE UNAFFECTED DURING THE IRRADIATION OF THE PEAKS AT 5.13 AND 5.68 P.P.M. ASSUMING THAT THE PEAKS AT 5.13 AND 5.68 P.P.M. ARE PRODUCED BY THE BENZYLIC PROTON, THEN THE PEAKS A AND B MAY BE ASSIGNED TO THE C-7 PROTON AND THE PEAKS C AND D TO THE C-10 PROTON.

THESE RESULTS AS WELL AS THE SPIN DECOUPLING EXPERIMENTS WITH 46 SHOW THAT THE TWO PEAKS FORMED BY THE BENZYLIC PROTON ARE READILY DECOUPLED FROM THE C-7 PROTON RESONANCES. SPIN DECOUPLING EXPERIMENTS WITH 6-HYDROXYCRINAMINE AND HAEMANTHIDINE REVEALED THAT THE PEAKS AT 5.58 P.P.M. ARE COUPLED TO THE SMALLER PEAKS AT 6.98 P.P.M. AND THE LARGER PEAKS AT 5.00 P.P.M. ARE COUPLED TO THE PEAKS AT 6.82 P.P.M.

THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE-6,11-D₂ (55) SUBSTANTIATES MUCH OF THE ABOVE DISCUSSION. THE SPECTRUM (FIG. 13b) IS VERY SIMILAR TO THAT OF 6-HYDROXYCRINAMINE EXCEPT

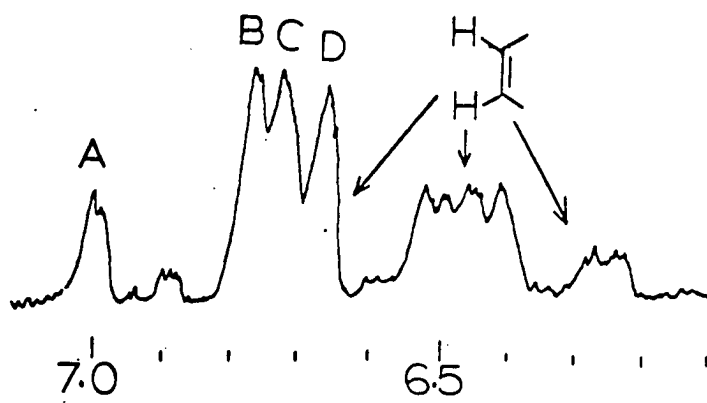
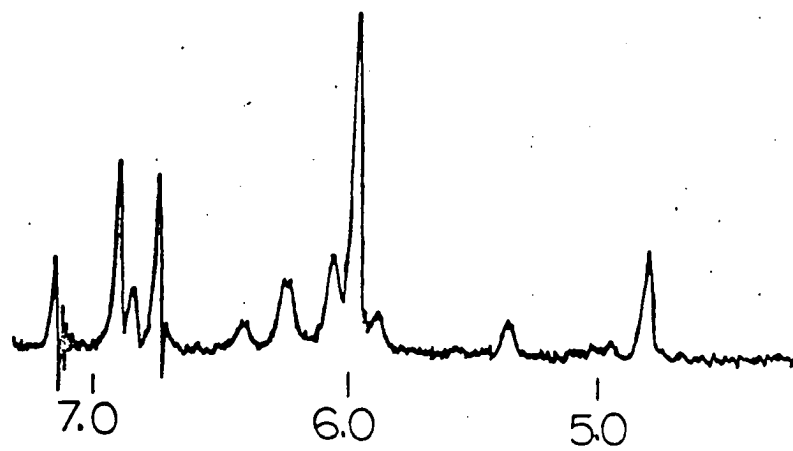
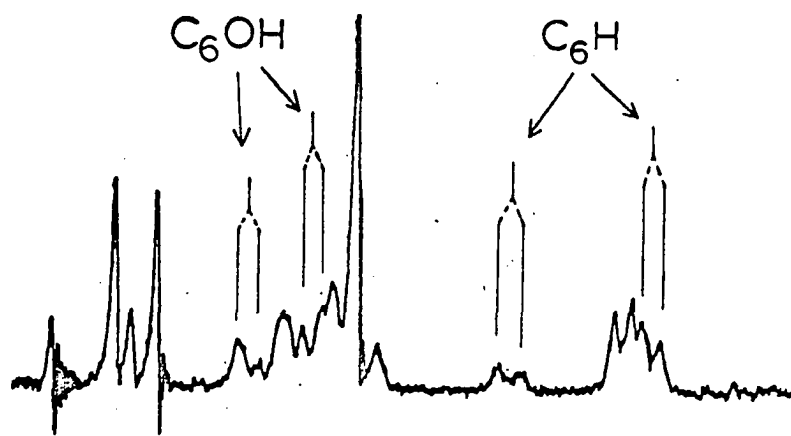
THAT THERE ARE NO NO PEAKS AT 5.00 AND 5.58 P.P.M. AND THE PEAK AT 4.1 P.P.M. IS REDUCED IN INTENSITY. THE PEAK AT 6.97 P.P.M. IS STILL PRESENT. THIS RESULT SHOWS THAT THE PEAKS AT 5.00 AND 5.58 P.P.M. IN THE SPECTRUM OF 6-HYDROXYCRINAMINE ARE PRODUCED SOLELY BY THE PROTON AT C-6. IN SUMMARY, THE DUAL CHEMICAL SHIFT OF THE BENZYLIC PROTON IS OBSERVED ONLY IN COMPOUNDS CONTAINING A C-6 HYDROXYL AND IS INDEPENDENT OF A DOUBLE BOND IN RING C OR SUBSTITUTION AT C-3 OR C-11. THE 6-HYDROXY COMPOUNDS ALL REACT AS IF THEY WERE ONE COMPOUND AND PURE.

RECENTLY IT WAS SHOWN THAT IN DIMETHYLSULFOXIDE PRIMARY, SECONDARY AND TERTIARY ALCOHOLS MAY BE CLASSIFIED ACCORDING TO THE SHAPE OF THE PEAK(S) PRODUCED BY THE HYDROXYL PROTON IN THEIR N.M.R. SPECTRA. ⁴⁴ IN DIMETHYLSULFOXIDE HYDROXYL PROTONS BECOME HYDROGEN BONDED TO THE SOLVENT WHICH REDUCES THE INTERMOLECULAR EXCHANGE RATE. THIS EFFECT IS EVIDENT IN THE N.M.R. SPECTRUM SINCE COUPLING IS FOUND BETWEEN THE HYDROXYL PROTON AND PROTONS ON THE ADJACENT CARBON. THUS PRIMARY HYDROXYLIC PROTONS GIVE RISE TO TRIPLETS, SECONDARY HYDROXYLIC PROTONS PRODUCE DOUBLETS AND TERTIARY ALCOHOLS GIVE A SINGLET PEAK. ⁴⁴ THE ASSIGNMENTS CAN BE VERIFIED BY ADDING DEUTERIUM OXIDE TO THE SAMPLE. THIS CAUSES DEUTERIUM-HYDROGEN EXCHANGE TO TAKE PLACE AND THE PREVIOUSLY NOTED COUPLING IN THE SPECTRUM DISAPPEARS ALONG WITH THE HYDROXYL PROTON PEAKS.

THE LOWER FIELD REGION OF THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE IN DIMETHYLSULFOXIDE IS SHOWN IN FIG. 14A. THE

FIG. 14: NUCLEAR MAGNETIC RESONANCE SPECTRA

- A: 6-HYDROXYCRINAMINE (35) IN DIMETHYLSULFOXIDE
- B: 35 + DEUTERIUM OXIDE IN DIMETHYLSULFOXIDE
- C: EXPANDED LOW FIELD REGION OF APOHAEMANTHIDINE

PPM (δ)

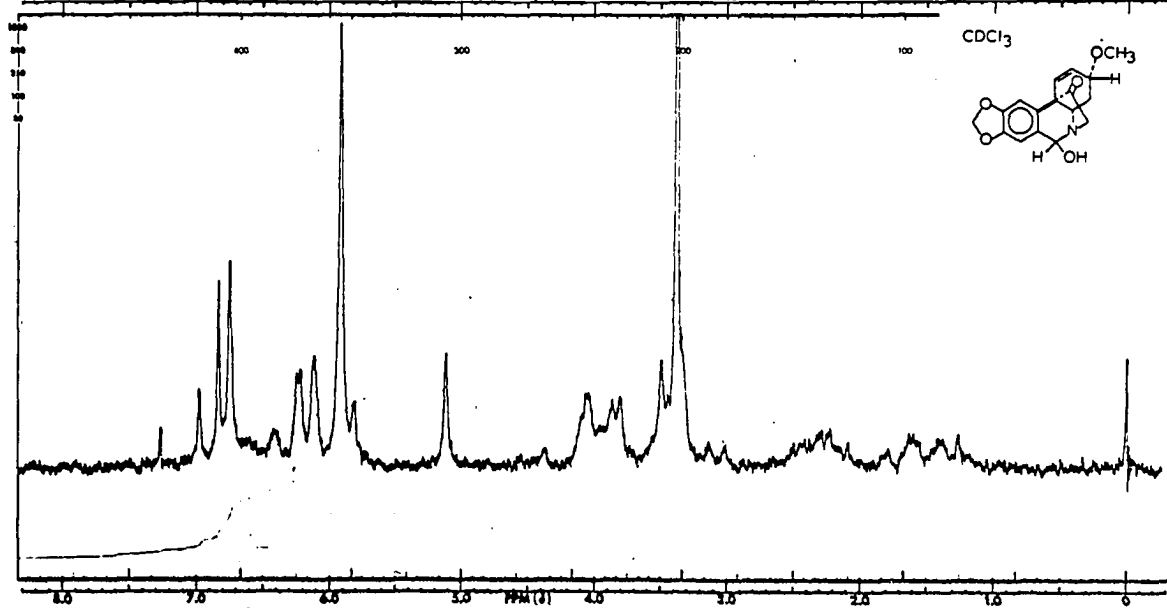
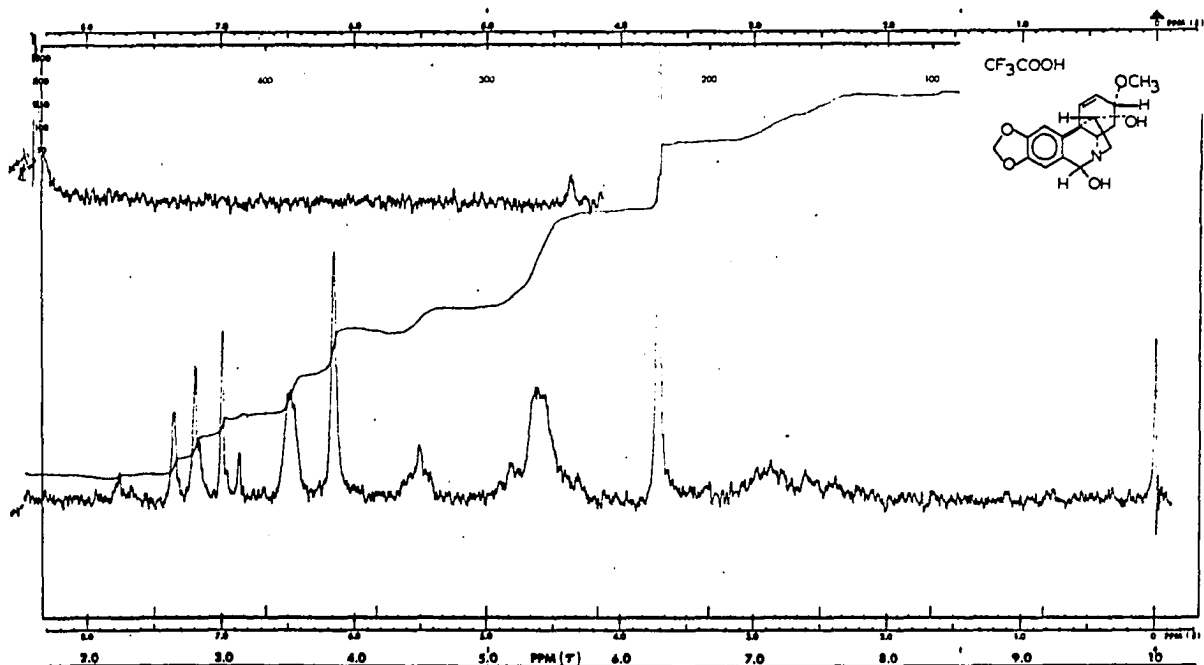
UPPER SPECTRUM SHOWS A COMPLEX ARRAY OF DOUBLETS, HOWEVER THE ADDITION OF DEUTERIUM OXIDE GREATLY SIMPLIFIES THE SPECTRUM AS SHOWN IN FI. 14B. CAREFUL EXAMINATION OF THE UPPER SPECTRUM REVEALS THAT THERE ARE FIVE DOUBLETS PRESENT. THREE OF THESE DOUBLETS DISAPPEAR UPON DEUTERATION AND TWO BECOME SINGLETS. THIS LEADS TO THE ASSIGNMENT SHOWN, I. E. THE C-6 PROTON, WHOSE RESONANCES ARE AT 4.9 AND 5.6 P.P.M., IS ATTACHED TO A CARBON BEARING A HYDROXYL GROUP WHOSE PROTON GIVES RISE TO DOUBLETS AT 6.1 AND 6.3 P.P.M. THE REMAINING DOUBLET AT 5.0 P.P.M. IS PRODUCED BY THE C-11 HYDROXYL PROTON. THESE DATA ESTABLISH WITH CERTAINTY THAT THE TWO COMPONENTS OF THE MIXTURE ARE SECONDARY BENZYLIC ALCOHOLS.

FURTHER SOLVENT EFFECTS WERE NOTED WHEN AN N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE IN TRIFLUOROACETIC ACID WAS OBTAINED (FIG. 15A). 6-HYDROXYCRINAMINE WAS FOUND TO BE STABLE IN TRIFLUOROACETIC ACID FOR THREE DAYS AND AT THAT TIME THE ALKALOID WAS RECOVERED AND FOUND TO BE IDENTICAL WITH THE ORIGINAL ALKALOID. THE HIGH DEGREE OF PROTONATION OF THE ELECTRONEGATIVE ATOMS HAS A PRONOUNCED EFFECT UPON THE N.M.R. SPECTRUM. THE AROMATIC REGION CONTAINS FIVE PEAKS. THE OLEFINIC PROTONS GIVE RISE TO A PEAK AT 6.5 P.P.M. AND THE METHYLENEDIOXY PROTON PEAK HAS SHIFTED TO 6.10 P.P.M. THE MULTIPLY AT 5.5 P.P.M. IS TENTATIVELY ASSIGNED TO THE 4A PROTON. THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE-6-D WAS SIMILAR TO THAT OF 6-HYDROXYCRINAMINE EXCEPT THAT THE TWO LOWEST FIELD PEAKS WERE ABSENT. SPIN DECOUPLING EXPERIMENTS SHOWED THAT THE SMALL PEAKS AT 7.74

FIG. 15: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6-HYDROXYCRINAMINE (35)

B: 6-HYDROXY-11-OXOCRINAMINE (58)



AND 6.81 P.P.M. ARE COUPLED AS ARE THE LARGER PEAKS AT 7.35 AND 6.94 P.P.M. NO HYDROGEN DEUTERIUM EXCHANGE OCCURRED OVER A PERIOD OF 24 HOURS. THUS THE DUAL CHEMICAL SHIFT PHENOMENA IS APPARENTLY INDEPENDENT OF THE DEGREE OF PROTONATION OF THE C-6 HYDROXYL GROUP OR THE AMINO NITROGEN. THE ADDITION OF A FEW DROPS OF TRIETHYLAMINE TO THE SAMPLE OF 6-HYDROXYCRINAMINE IN DEUTERIOCHLOROFORM HAD NO EFFECT UPON THE SHAPE OR CHEMICAL SHIFTS OF THE PEAKS AT 5.00 AND 5.58 P.P.M. ACID AND BASE CATALYSIS DOES NOT SEEM TO BE A FACTOR EFFECTING THE RATIO OF THE TWO COMPONENTS OF 6-HYDROXYCRINAMINE.

AS MIGHT BE EXPECTED, THE N.M.R. SPECTRUM (FIG. 15B) OF 6-HYDROXY-11-OXOCRINAMINE (58) IS SIMILAR TO THOSE OF ALL COMPOUNDS CONTAINING A C-6 HYDROXYL GROUP, WITH ONLY SLIGHT BUT SIGNIFICANT VARIATIONS. THREE PEAKS APPEAR IN THE AROMATIC PROTON REGION OF THE SPECTRUM AND THE OLEFINIC PROTONS FORM THE AB PART OF AN ABX PATTERN. THE METHYLENEDIOXY AND METHOXYL PROTONS GIVE RISE TO SINGLET S AT 5.97 AND 3.38 P.P.M., RESPECTIVELY. THE TWO PEAKS ASSIGNED TO THE C-6 PROTON HAVE SHIFTED DOWNFIELD TO 5.13 AND 5.80 P.P.M. THE DIFFERENCE IN CHEMICAL SHIFT OF THE TWO PEAKS IS NOW 0.67 P.P.M. WHICH IS LARGER THAN THE DIFFERENCE IN CHEMICAL SHIFT (0.058 P.P.M.) OF THE TWO PEAKS IN THE SPECTRUM OF THE PARENT ALKALOID. THESE DATA SUGGEST THAT THE CARBONYL GROUP IN THE PYRROLIDINE RING, EITHER BECAUSE OF THE CHANGE IN HYBRIDIZATION OR AS AN ANISOTROPIC EFFECT, PRODUCES A DESHIELDING OF THE BENZYLIC PROTON. IN ADDITION THE DESHIELDING OF ONE OF THE COMPONENT C-6 PROTONS

IS GREATER THAN FOR THE OTHER.

A SIMILAR EFFECT WAS NOTED IN THE CHEMICAL SHIFTS OF THE BENZYLIC PROTONS OF CRINAMINE AND 11-OXOCRINAMINE.³⁰ THE C-6 PROTONS OF CRINAMINE PRODUCE AN AB PATTERN ($J_{AB} = 17.0$ C.P.S.) WITH CHEMICAL SHIFTS AT 3.65 AND 4.24 P.P.M. WHEREAS THE CHEMICAL SHIFTS OF THE C-6 PROTONS OF 11-OXOCRINAMINE ARE 3.80 AND 4.55 P.P.M. THE HIGHER FIELD PROTON HAS SHIFTED 0.15 P.P.M. AND THE LOWER FIELD PROTON HAS SHIFTED 0.31 P.P.M. SIMILAR DIFFERENCES WERE NOTED IN THE N.M.R. SPECTRA OF HAEMANTHAMINE AND 11-OXOHAEMANTHAMINE.³⁰ AN EXAMINATION OF MODELS REVEALS THAT IN THE 11-OXO COMPOUNDS THE CARBONYL GROUP IS CLOSER TO ONE OF THE C-6 PROTONS THAN THE OTHER, WHICH SUGGESTS THAT THE FORMER PROTON PRODUCES THE LOWER FIELD DOUBLET IN THE AB PATTERN. SIMILARLY, THE LOWEST FIELD PEAK ASSIGNED TO THE BENZYLIC PROTON OF THE 6-HYDROXY ALKALOIDS IS LOCATED IN AN ENVIRONMENT CLOSER TO THE C-11 POSITION.

IN ANOTHER EXPERIMENT THE RATIOS OF THE AREAS OF THE PEAKS AT 5.00 AND 5.58 P.P.M. WERE STUDIED DURING THE PROCESS OF CONVERTING THE 6-HYDROXYL GROUP TO A CARBONYL GROUP. 6-HYDROXYCRINAMINE WAS DISSOLVED IN CHLOROFORM AND STIRRED WITH MANGANESE DIOXIDE. AT GIVEN INTERVALS, ALIQUOTS OF THE MIXTURE WERE TAKEN, THE MANGANESE DIOXIDE REMOVED BY FILTRATION AND A N.M.R. SPECTRUM OBTAINED. AN EXAMINATION OF THE INTEGRALS OF THE AREAS OF THE PEAKS AT 5.00 AND 5.58 P.P.M. REVEALED THAT THE RATIOS OF THE AREAS OF THE TWO PEAKS REMAINED RELATIVELY CONSTANT DURING THE OXIDATION. IF TWO NONINTER-

CONVERTIBLE COMPONENTS EXIST IN SOLUTION A DIFFERENTIAL RATE OF OXIDATION MIGHT BE OBSERVED. HOWEVER, IF THE SUBSTANCES ARE INTERCONVERTIBLE, NO DIFFERENTIAL RATE OF OXIDATION WOULD BE EXPECTED.

TO SUBSTANTIATE THE PROPOSAL THAT THE TWO COMPONENTS ARE INTERCONVERTIBLE, VARIABLE TEMPERATURE N.M.R. EXPERIMENTS WERE PERFORMED. NO CHANGE OCCURRED IN THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE AT -30° . AT 40° (FIG. 16) THE N.M.R. SPECTRUM OF 6-HYDROXYCRINAMINE IS ESSENTIALLY THAT FOUND AT ROOM TEMPERATURE. AT 60° , 80° AND 100° THE PEAKS ASSIGNED TO THE BENZYLIC PROTON BROADEN; THE TWO PEAKS ASSIGNED TO THE C-7 PROTON COALESCE AND THE PEAK ASSIGNED TO THE C-10 PROTON SHARPENS. THESE DATA SUGGEST THAT AT ROOM TEMPERATURE THE RATE OF INTERCONVERSION OF EPIMERS IS SLOW (CERTAINLY LESS THAN 1 SEC^{-1}) BUT SUFFICIENTLY FAST TO PRECLUDE THE ISOLATION OF EITHER COMPONENT. THESE EXPERIMENTS SHOW THAT 6-HYDROXYCRINAMINE AND PROBABLY ALL 6-HYDROXY COMPOUNDS EXIST IN SOLUTION AS AN EQUILIBRATING MIXTURE OF COMPONENTS.

DISCUSSION OF THE EQUILIBRIA

THE DUAL CHEMICAL SHIFTS OF THE BENZYLIC PROTON IN THE N.M.R. SPECTRA OF THE 6-HYDROXY ALKALOIDS CONTAINING THE 5,10B-ETHANOPHENANTHRIDINE NUCLEUS APPEARS TO BE A GENERAL PHENOMENA. TWO POSSIBILITIES EXIST THAT COULD EXPLAIN THE OCCURRENCE OF THE DUAL CHEMICAL SHIFTS. THE 6-HYDROXYL GROUP AND C-6 PROTON COULD ACHIEVE EITHER TWO CONFORMATIONS OR TWO DIFFERENT CONFIGURATIONS. HOWEVER IT IS DIFFICULT TO RATIONALIZE THIS

PHENOMENA ON CONFORMATIONAL GROUNDS. ALKALOIDS WITH THE 5,10B-ETHANOPHENANTHRIDINE MOIETY ARE KNOWN TO BE SEMIRIGID.⁴³ RINGS A, B AND D ARE INFLEXIBLE BECAUSE OF THE AROMATIC AND BICYCLIC NATURE OF THE SYSTEM. ATOMS C-6, C-6A, C-10A, C-10B AND N-5 ARE COPLANAR WITH THE AROMATIC RING AND SUBSTITUENTS AT C-6 ARE BISECTED BY THIS PLANE. ONLY RING C HAS MOBILITY AND THIS IS LIMITED TO THE HALF CHAIR-HALF BOAT INTERCONVERSION. IN APOHAEMANTHIDINE (22) EVEN THIS FLEXIBILITY IS REMOVED.

THE SECOND ALTERNATIVE, I. E. CONFIGURATIONAL CHANGE, ALSO IS NOT EASILY EXPLAINED. IF THE TWO COMPONENTS ARE EPI-MERIC THEN THE N.M.R. EXPERIMENTS WITH 6-HYDROXYCRINAMINE IN DIMETHYLSULFOXIDE AND THE CHEMICAL SHIFTS OF THE C-6 PROTON PEAKS OF 6-HYDROXY-11-OXOCRINAMINE ARE READILY EXPLAINED. IN THE FIRST EXPERIMENT BOTH COMPONENTS WERE SHOWN TO BE SECONDARY ALCOHOLS AND IN THE SECOND EXPERIMENT IT WAS CONCLUDED THAT THE C-6 PROTON OF THE TWO COMPONENTS WAS IN A SIMILAR ENVIRONMENT AS THE C-6 METHYLENE PROTONS OF CRINAMINE. IF THE TWO COMPONENTS ARE EPIMERIC THEN THE ALDEHYDE 59 MUST HAVE AT LEAST MOMENTARY EXISTENCE. HOWEVER NO AMOUNT OF ALDEHYDE HAS EVER BEEN DETECTED BY N.M.R., INFRARED OR ULTRAVIOLET SPECTROSCOPY. BOTH THE FUCHSIN ALDEHYDE REAGENT^{45, p. 114} AND TOLLEN'S REAGENT^{45, p. 162} GIVE NEGATIVE ALDEHYDE TESTS EVEN AFTER PROLONGED REACTION TIME. ALL 6-HYDROXY COMPOUNDS ARE UNREACTIVE TOWARD LITHIUM ALUMINUM HYDRIDE, SODIUM BOROHYDRIDE AND HYDROXYLAMINE. MODELS SHOW THAT THE C-6 POSITION IS SEVERELY HINDERED WHICH MAY EXPLAIN THE ABSENCE OF ATTACK AT

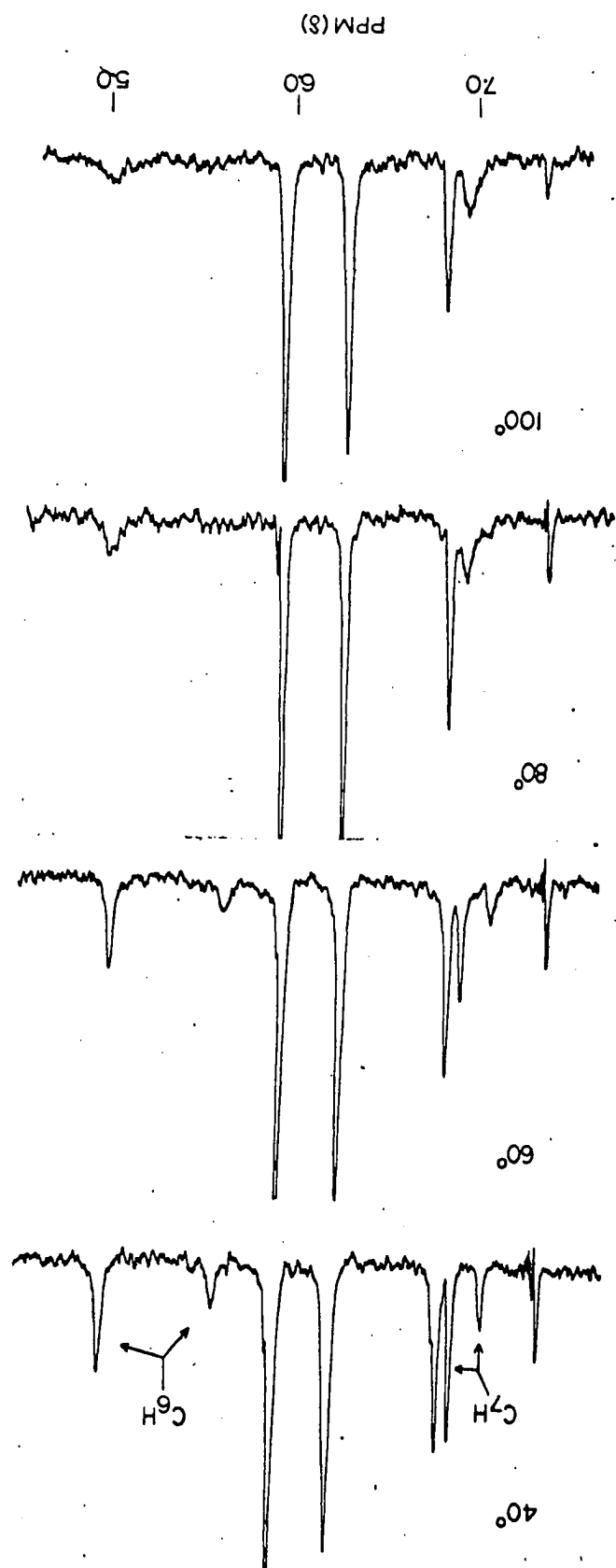
FIG. 16: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 6-HYDROXYCRINAMINE (35) AT 40°

B: 35 AT 60°

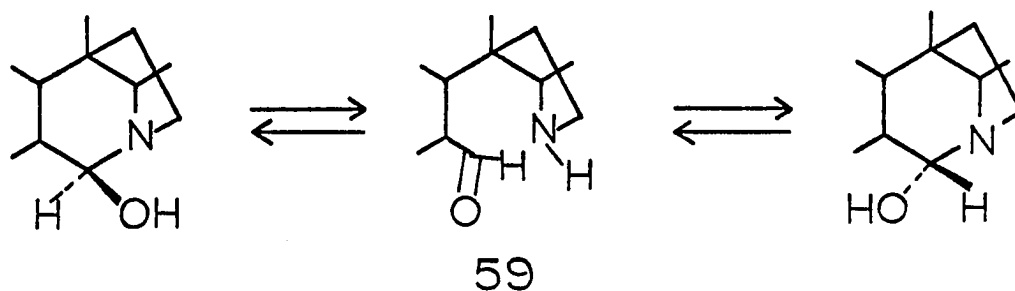
C: 35 AT 80°

D: 35 AT 100°



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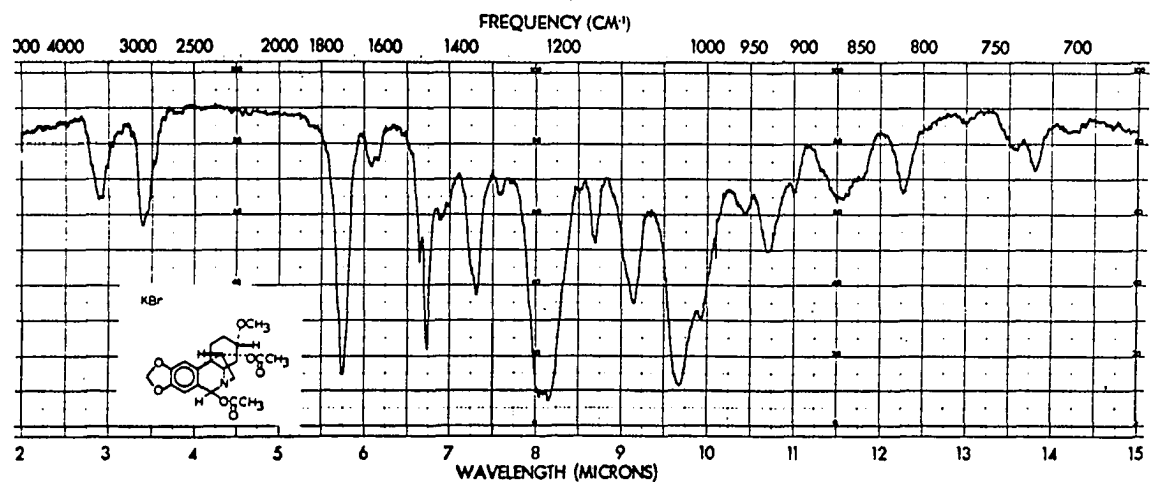
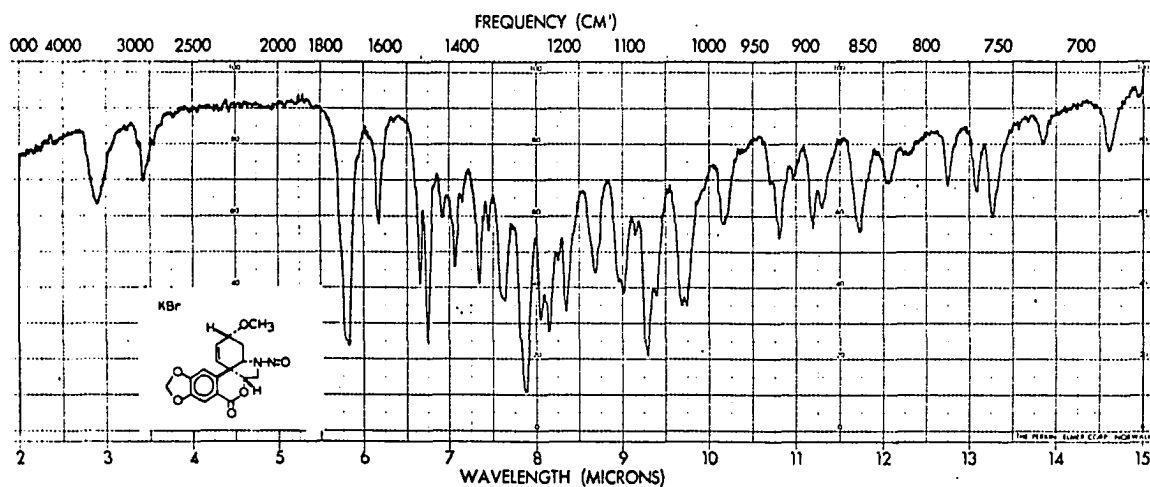
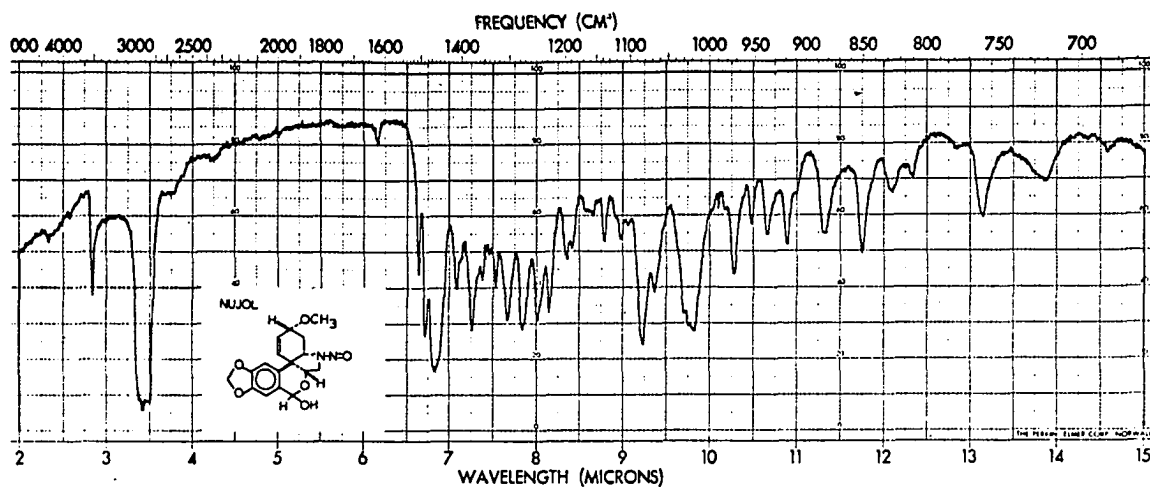
THE CONVERSION OF HAEMANTHIDINE TO N-DEMETHYLTAZETTINE (W. C. WILDMAN, PRIVATE COMMUNICATION) IN CONCENTRATED BASE AND HEATING SUGGESTS THAT AN INTERMEDIATE ALDEHYDE MAY BE INVOLVED. GENERALLY HAEMANTHIDINE MUST BE N-METHYLATED BEFORE THE RING OPENING REACTION TAKES PLACE. THE VIGOROUS CONDITIONS OF THIS CONVERSION PROBABLY PROMOTE THE FORMATION OF THE ALDEHYDE INTERMEDIATE.



ALTHOUGH ALDEHYDIC REAGENTS ARE UNREACTIVE TOWARD THE 6-HYDROXYL GROUP, NITROUS ACID REACTS WITH 6-HYDROXYCRINAMINE TO GIVE A N-NITROSO DERIVATIVE. IT IS WELL KNOWN THAT NITROUS ACID DOES NOT REACT WITH TERTIARY AMINES⁴⁶, P. 508 AND A REACTION IN THIS CASE MAY MEAN THAT THE AMINE 59 IS PRESENT IN THE SOLUTION. HOWEVER THE PRESENCE OF BOTH ACID AND BASIC COMPONENTS IN THE SOLUTION MAY CATALYTICALLY OPEN THE B RING TO FORM AN ALDEHYDE AT THE SAME TIME NITROSATION IS TAKING PLACE. A SIMILAR REACTION IS THE N-METHYLATION OF HAEMANTHIDINE WITH FORMALDEHYDE AND FORMIC ACID.⁴⁷ AGAIN THE SECONDARY AMINE MAY BE FORMED AS A RESULT OF SIMULTANEOUS N-METHYLATION AND RING OPENING.

FIG. 17: INFRARED SPECTRA

- A: N-NITROSO-6-HYDROXYCRINAMINE (60)**
- B: N-NITROSO-6-OXOCRINAMINE (61)**
- C: 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE
(46) ACETYLATED AT 110°**



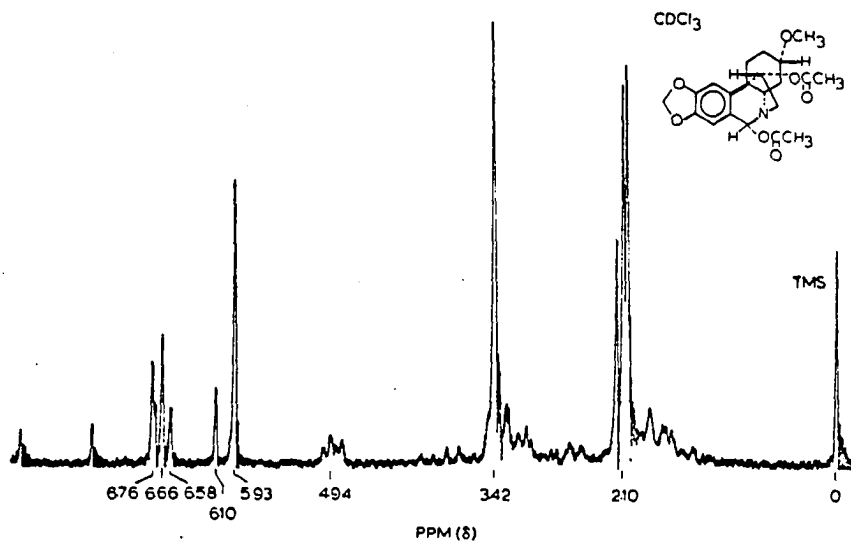
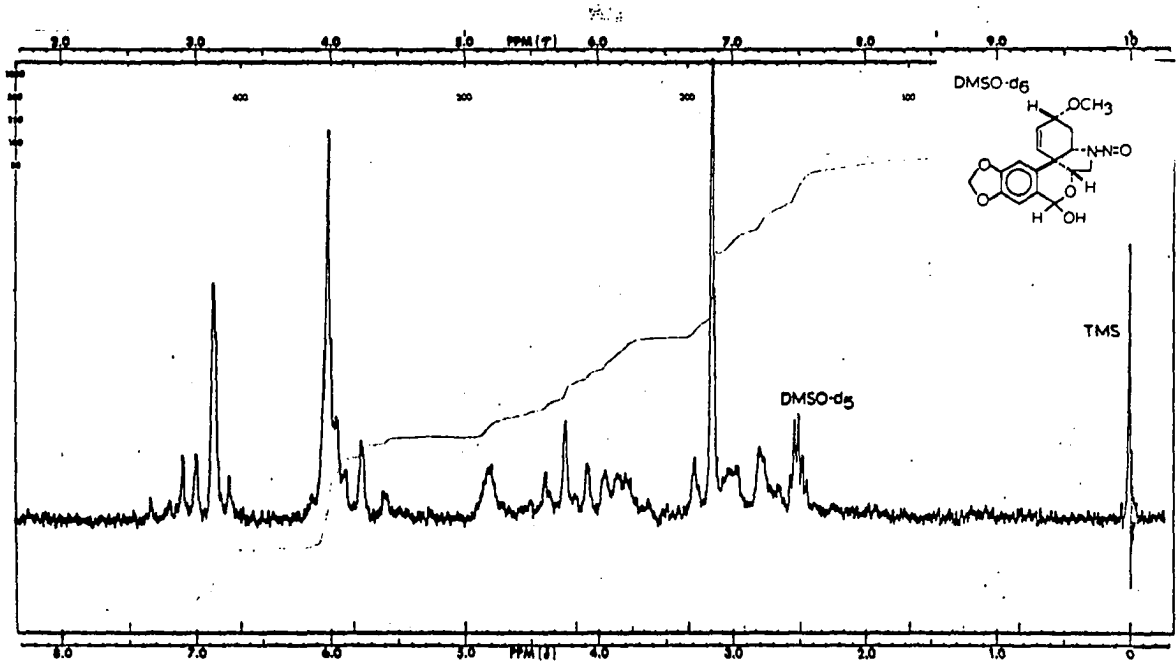
THE REACTION PRODUCT OF 6-HYDROXYCRINAMINE WITH NITROUS ACID IS NOT AN ALDEHYDE. THE INFRARED SPECTRUM (FIG. 17A) DOES NOT SHOW THE EXPECTED CARBONYL BAND AND THE ULTRAVIOLET ABSORPTION AT 239 AND 290 $m\mu$ IS NOT CHARACTERISTIC OF AN AROMATIC ALDEHYDE. THE STRONG HYDROXYL ABSORPTION (2.69 μ) IN THE INFRARED SUGGESTED THAT THE HEMIACETAL 60 WAS THE ACTUAL PRODUCT. THE N.M.R. SPECTRUM OF 60 IN DIMETHYLSULFOXIDE- D_6 (FIG. 18A) WAS INTERESTING BECAUSE APPARENTLY TWO EPIMERS ARE PRESENT IN THIS COMPOUND ALSO. ALL FOUR PEAKS IN THE 7-7.5 P.P.M. REGION DISAPPEAR UPON DEUTERATION. THE SMALLER AROMATIC PROTON PEAK AT 6.74 P.P.M. INTEGRATES FOR AN AREA CORRESPONDING TO THE AREA OF THE SMALLER DOUBLET AT 7.32 P.P.M. THE BENZYLIC PROTON DOUBLET(S) IS SUPERIMPOSED UPON THE METHYLENEDIOXY AND OLEFINIC PROTON PEAKS IN THE 6 P.P.M. REGION. THE BROAD PEAK AT 4.8 P.P.M. IS ASSIGNED TO THE C-11 PROTON AND THE TRIPLET AT 4.3 P.P.M. IS ASSIGNED TO THE C-12 PROTONS. THE METHOXYL PROTONS GIVE RISE TO THE SINGLET AT 3.15 P.P.M. THIS PEAK IS FURTHER UPFIELD THAN MOST OF THE METHOXYL PROTON RESONANCES (3.29 - 3.45 P.P.M.) OBSERVED. THE CAUSE FOR THIS SHIFT IS PROBABLY A SHIELDING EFFECT PRODUCED BY THE ANISOTROPY OF THE N-NITROSO GROUP. AN EFFECT SUCH AS THIS COULD ONLY BE EXPECTED IF THE METHOXYL AND AMINO GROUP ARE CIS. THIS OBSERVATION SUPPORTS THE CIS HYDROXYL AND AMINO GROUPS IN ISOTAZETTINOL AS ORIGINALLY PROPOSED.¹⁰

FURTHER SUPPORT FOR THE STRUCTURE OF 60 WAS OBTAINED BY THE OXIDATION OF THE HEMIACETAL TO THE LACTONE 61 WITH MANGANESE

FIG. 18: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: N-NITROSO-6-HYDROXYCRINAMINE (60)

**B: 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46)
ACETYLATED AT 110°**



CONVERSION. SINCE THIS WAS NOT OBSERVED, A CONFORMATIONAL EQUILIBRIUM OF THE 6-HYDROXY AND 6-ACETOXY COMPOUNDS IS DEEMED UNLIKELY.

IN ANOTHER EXPERIMENT DIHYDRO-6-HYDROXYCRINAMINE WAS ACETYLATED WITH ACETIC ANHYDRIDE IN PYRIDINE AT 110° . THE PURPOSE OF THE EXPERIMENT WAS TO TRAP A DIFFERENT EQUILIBRIUM MIXTURE OF EPIMERIC ALCOHOLS THAN THAT PRESENT AT ROOM TEMPERATURE. ALTHOUGH THE INFRARED SPECTRUM OF THIS 6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (FIG. 17C) WAS NEARLY IDENTICAL TO THAT OF THE ROOM TEMPERATURE ACETYLATED PRODUCT (FIG. 9A), THE N.M.R. SPECTRUM (FIG. 18B) EXHIBITED A LARGER PEAK AT 6.58 P.P.M. THIS DIFFERENCE WAS MAINTAINED EVEN UPON DISTILLATION, WHICH SUPPORTS THE PROPOSAL THAT TWO NONINTERCONVERTIBLE SUBSTANCES ARE PRESENT. DESPITE THE FACT THAT ACTUAL SEPARATION OF THE EPIMERIC ACETATES HAS NOT BEEN ACHIEVED, ALL ARE APPARENTLY MIXTURES.

IN CONCLUSION SEVERAL COMMENTS WILL BE PRESENTED WITH REGARD TO THE APPARENT EPIMERIC EQUILIBRIUM SHOWN BY THE 5,10B-ETHANOPHENANTHRIDINE ALKALOIDS CONTAINING A HYDROXYL GROUP AT THE SIX POSITION.

THE EPIMERIC PROTONS OF THE COMPONENTS OF THE 6-HYDROXYCRINAMINE EQUILIBRIUM GIVE RISE TO QUITE DIFFERENT CHEMICAL SHIFTS (5.00 AND 5.58 P.P.M.) HOWEVER THE DIFFERENCE COMPARES FAVORABLY WITH THE CHEMICAL SHIFTS OF THE METHYLENE PROTONS OF THE C-6 POSITION OF CRINAMINE (3.65 AND 4.24 P.P.M.).³⁰ IT SEEMS RATHER UNLIKELY THAT THE MAGNETIC ANISOTROPY OF THE

AROMATIC RING PLAYS A ROLE IN PRODUCING THE LARGE CHEMICAL SHIFT DIFFERENCE OF THE EPIMERIC PROTONS BECAUSE ITS PLANE BISECTS THE ANGLE BETWEEN SUBSTITUENTS AT C-6. ALTERNATIVELY THE P ELECTRON PAIR ON NITROGEN COULD PRODUCE AN ANISOTROPIC ENVIRONMENT, HOWEVER THE CHEMICAL SHIFT DIFFERENCE STILL EXISTS IN TRIFLUOROACETIC ACID, IN WHICH THE NITROGEN IS SURELY PROTONATED, THUS CANCELLING ANY EFFECT THE ELECTRON PAIR MAY HAVE. STILL ANOTHER POSSIBLE CAUSE OF THE DIFFERENCE IN CHEMICAL SHIFT OF THE EPIMERIC PROTONS IS SIMPLY THE ASYMMETRIC ENVIRONMENT (EXO VERSUS ENDO) INHERENT IN THE RING SYSTEM. AT THE TIME OF THIS WRITING, THIS EXPLANATION SEEMS MOST PLAUSIBLE.

THE EVIDENCE PRESENTED SHOWS THAT 6-HYDROXYCRINAMINE AND RELATED 6-HYDROXY COMPOUNDS EXIST COMPLETELY IN THE CARBINOL-AMINE FORMS RATHER THAN THE POTENTIAL HEMIACETAL OR FREE ALDEHYDE FORMS. AN EXPLANATION FOR THIS OBSERVATION MAY BE OBTAINED FROM THE STUDY MODELS OF THESE COMPOUNDS.* IF THE C-6-NITROGEN BOND IS BROKEN, IT BECOMES IMMEDIATELY EVIDENT THAT THE DEGREES OF FREEDOM OF MOVEMENT OF THE AMINO GROUP ARE FEW. ANY ATTEMPTED ROTATION AROUND THE C-10A-C-10B BOND CREATES STRONG STERIC INTERACTIONS BETWEEN THE HALVES OF THE MOLECULE AND/OR A DISTORTION OF THE BOND ANGLES. HOWEVER WHEN THE C-6-NITROGEN IS FORMED, THE MODELS INDICATE THAT THERE IS CONSIDERABLE BOND ANGLE STRAIN IN THE BICYCLIC RING SYSTEM. THE MINIMUM AMOUNT OF STRAIN SEEMS TO OCCUR WHEN THE C-6-NITROGEN

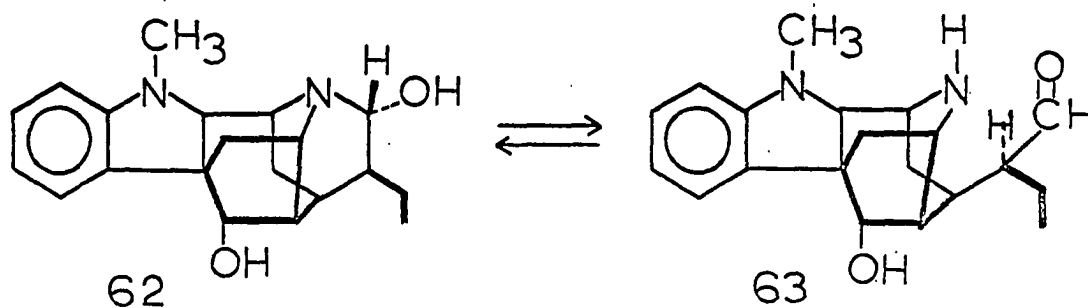
*DREIDING MODELS WERE USED.

DISTANCE IS APPROXIMATELY $1.7 \overset{\text{O}}{\text{Å}}$ INSTEAD OF THE MORE IDEAL $1.47 \overset{\text{O}}{\text{Å}}$.^{48, p. 112} THESE OBSERVATIONS SUGGEST THAT EVEN IF THE ALDEHYDE IS FORMED, ITS EXISTENCE WOULD BE SHORT LIVED BECAUSE OF THE CLOSE PROXIMITY OF THE NITROGEN. IN FACT THE EVIDENCE INDICATES THAT C-6-NITROGEN BOND FORMATION PRODUCES GREATER STABILITY THAN THE NONBONDED ROTAMERS; THE C-6-NITROGEN BOND PROBABLY NEVER GAINS FULL BOND ENERGY. THUS THE C-6-NITROGEN BOND MAY BE EASILY BROKEN, BUT BECAUSE OF THE PROXIMITY OF THE NITROGEN, A FREE ALDEHYDE IS NEVER OBSERVED. THIS POSTULATE EXPLAINS THE PRESENCE OF EPIMERS IN SOLUTION AS WELL AS THE ABSENCE OF AN ALDEHYDE GROUP.

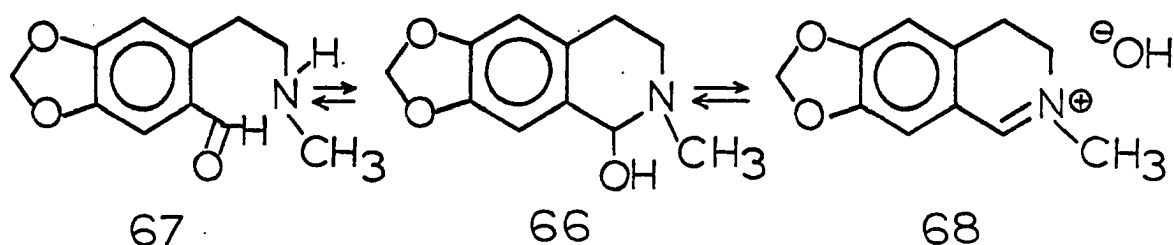
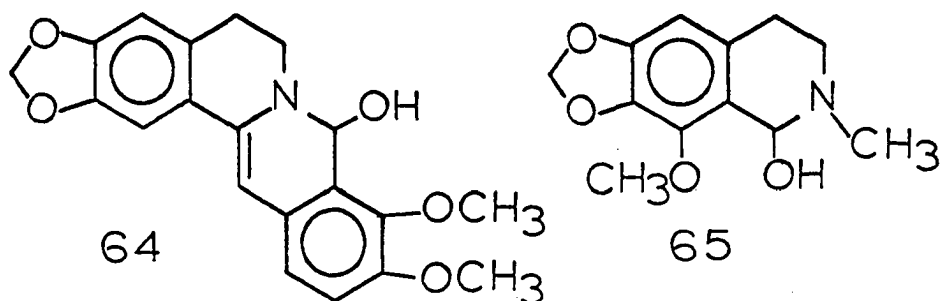
IF THE PHENOMENON OBSERVED IN THESE 6-HYDROXY ALKALOIDS IS ACTUALLY SPONTANEOUS EPIMERIZATION, THERE ARE FEW EXAMPLES FOR COMPARISON KNOWN. MOST EPIMERIZATIONS REQUIRE ACID OR BASE CATALYSIS WHEREAS THE EPIMERIZATION OBSERVED IN THESE CASES EXIST IN ACID OR BASE WITHOUT ANY OBSERVABLE CHANGE IN RATE. THE MUTAROTATION OF GLUCOSE IS A POSSIBLE ANALOGY TO THE 6-HYDROXY EPIMERIZATION, HOWEVER THE MUTAROTATION OF GLUCOSE IS CATALYZED BY ACID OR BASE AND THE INTERMEDIATE ALDEHYDE CAN BE TRAPPED WITH PHENYLHYDRAZINE TO GIVE THE FAMILAR OSAZONE. SINCE THE 6-HYDROXYCRINAMINE EQUILIBRIUM DOES NOT HAVE ANY OF THESE CHARACTERISTICS, THE VALIDITY OF SUCH A COMPARISON IS QUESTIONABLE.

AJMALINE (62) HAS SEVERAL FEATURES IN COMMON WITH THE 6-HYDROXYCRINAMINE TYPE OF ALKALOID.^{49, p. 789} AJMALINE CONTAINS A BRIDGEHEAD NITROGEN AND AN ADJACENT HYDROXYL GROUP IN

A 1-AZABICYCLO[2,2,2]OCTANE MOIETY. THE REACTIONS OBSERVED FOR THIS GROUPING ARE THOSE EXPECTED FOR THE ALCOHOL FROM 62 AND THE ALDEHYDE 63. THUS AJMALINE IS REDUCED UNDER WOLFF-KISHNER CONDITIONS OR BY POTASSIUM BOROHYDRIDE BUT FORMS AN O,O-DIACETATE UPON ACETYLATION. HOWEVER, THERE IS NO EVIDENCE FOR THE ALDEHYDE GROUP IN THE INFRARED. THE DIFFERENCE IN REACTIVITY OF 6-HYDROXYCRINAMINE AND AJMALINE IS PROBABLY BECAUSE IN AJMALINE THE ALDEHYDE GROUP IS FREE TO MOVE AWAY FROM THE AMINO NITROGEN, AND ASSUME ITS INTEGRITY. A FREE ALDEHYDE APPARENTLY DOES NOT EXIST WITH 6-HYDROXYCRINAMINE.

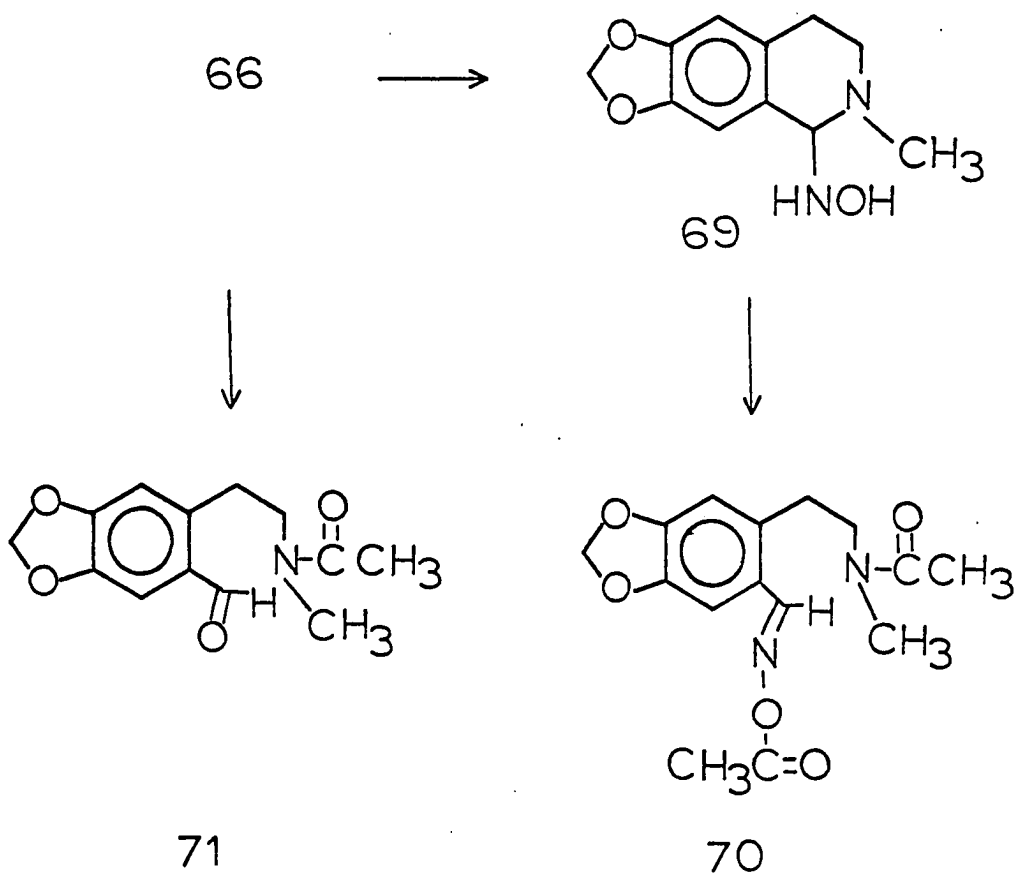


OTHER ALKALOIDS KNOWN TO CONTAIN CARBINOL-AMINE GROUPS ARE BERBERINE (64), COTARNINE (65) AND HYDRASTININE (66). UPON ANALYZING AVAILABLE EVIDENCE, BEKE⁵⁰ SUGGESTED THAT THERE IS NO EVIDENCE TO SUPPORT AN INTERMEDIATE ALDEHYDE IN THE POSSIBLE EQUILIBRIUM OF HYDRASTININE ($67 \rightleftharpoons 66 \rightleftharpoons 68$). RECENT WORK BY SCHNEIDER AND MÜLLER TENDS TO SUPPORT THIS PROPOSAL.⁵¹ IN THE SOLID STATE (KBR) THE INFRARED SPECTRUM SHOWS ABSORPTION AT 2.95 AND 5.97 μ CORRESPONDING TO HYDROXYL AND C=N STRETCHING FREQUENCIES. HYDRASTININE REACTS WITH HYDROXYLAMINE TO GIVE A SUBSTITUTED HYDROXYLAMINE (69) WHICH UPON ACET-



YLATION GIVES AN O,N-DIACETATE (70). ACETYLATION OF HYDRAS-
 TININE GIVES THE N-ACETYL DERIVATIVE 71. THESE REACTION PRO-
 DUCTS MAY BE INTERPRETED EITHER AS THE REACTION OF THE FREE
 ALDEHYDE OR AS A CATALYTIC FORMATION OF THE ALDEHYDE UNDER RE-
 ACTION CONDITIONS. SIMILAR REACTIONS ARE UNDERGONE BY COTAR-
 NINE⁵¹ BUT THE INFORMATION AVAILABLE ON BERBERINE DOES NOT
 CONCERN A POSSIBLE EQUILIBRIUM.

HYDRASTININE EXHIBITS DIFFERENT PROPERTIES FROM THOSE OF
 6-HYDROXYCRINAMINE OR AJMALINE, PROBABLY BECAUSE OF THE AD-
 DITIONAL STABILITY IT ATTAINS IN THE QUATERNARY HYDROXIDE
 FORM. THE STABILITY OF 3,4-DIHYDROISOQUINOLINES IS WELL
 KNOWN.^{52, p. 74}

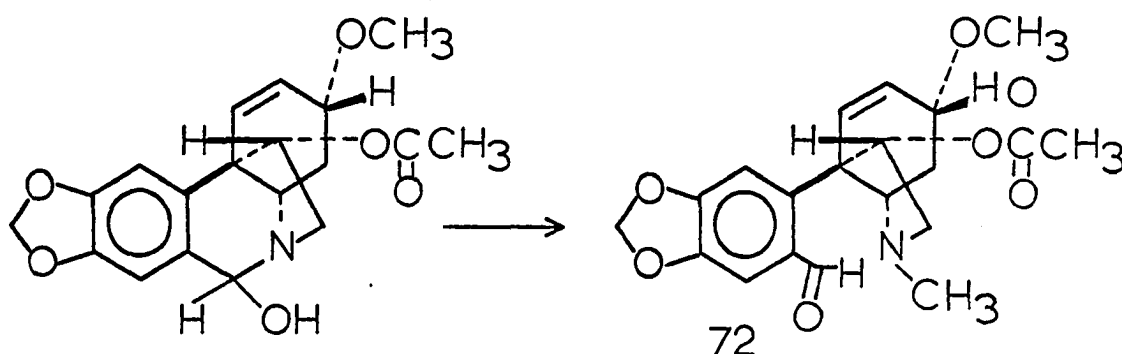


THE REACTIONS OF THESE OTHER ALKALOIDS CONTAINING THE CARBINOL AMINE GROUPING ARE PRESENTED AS A CONTRAST TO THOSE OF 6-HYDROXYCRINAMINE AND RELATED COMPOUNDS. NORMALLY IT WOULD BE EXPECTED THAT 6-HYDROXYCRINAMINE SHOULD SHOW SOME ALDEHYDIC PROPERTIES, BUT NONE ARE OBSERVED. THIS DATA ILLUSTRATES THE DIFFERENCE BETWEEN 6-HYDROXYCRINAMINE AND OTHER CARBINOL AMINE ALKALOIDS AND SHOWS WHY A DIFFERENT INTERPRETATION IS NEEDED TO EXPLAIN ITS REACTIVITY TOWARD VARIOUS REAGENTS.

OTHER REACTIONS OF 6-HYDROXYCRINAMINE DERIVATIVES

ISOLATION OF AN ALDEHYDE DERIVATIVE

IT SEEMED REASONABLE THAT 11-ACETYL-6-HYDROXYCRINAMINE SHOULD YIELD THE ALDEHYDE 72 UPON TREATMENT WITH METHYL IODIDE AND SUBSEQUENTLY, DILUTE BASE. THE ALDEHYDE SHOULD BE ISOLABLE BECAUSE THE 11-ACETYLATED ALCOHOL IS NOW UNREACTIVE. THE



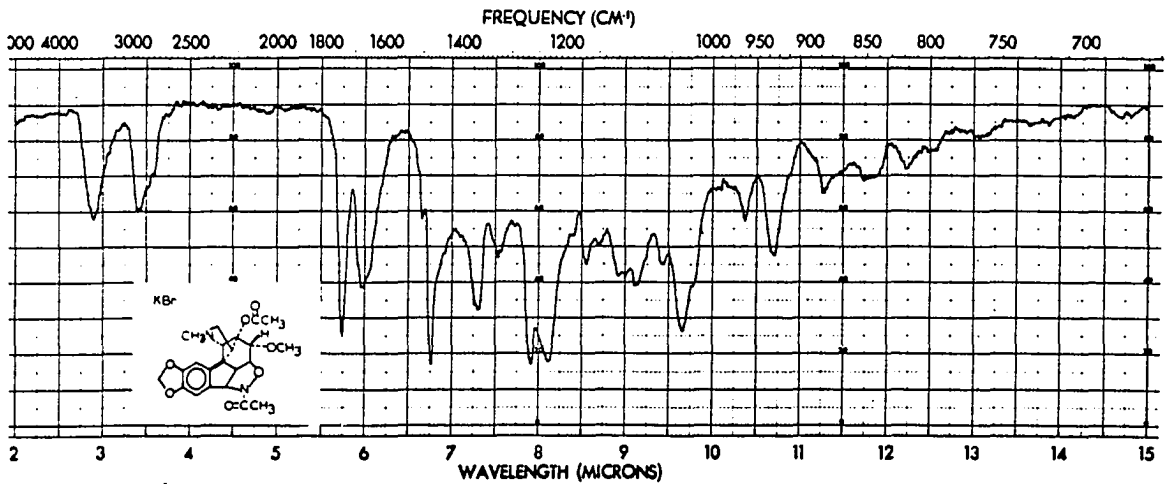
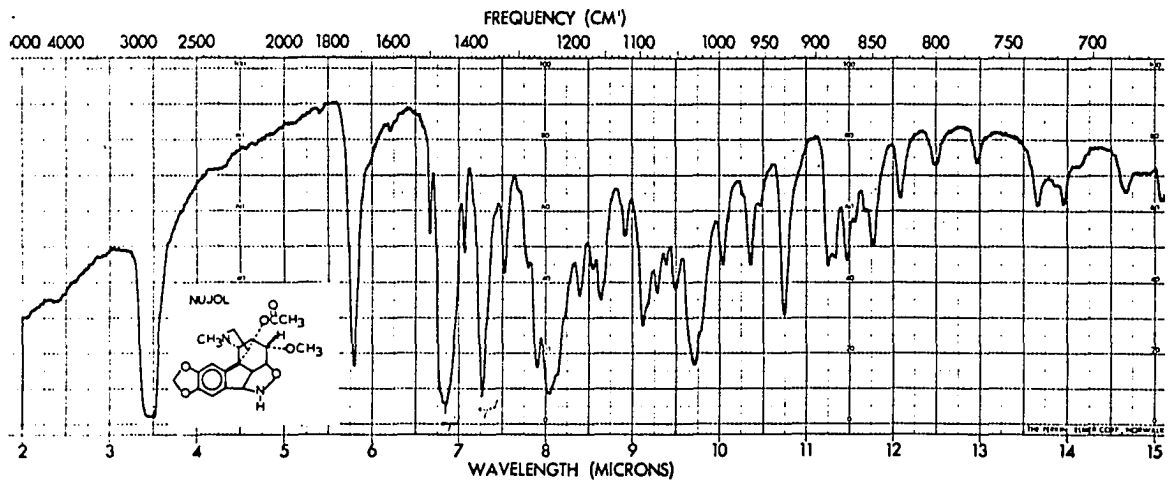
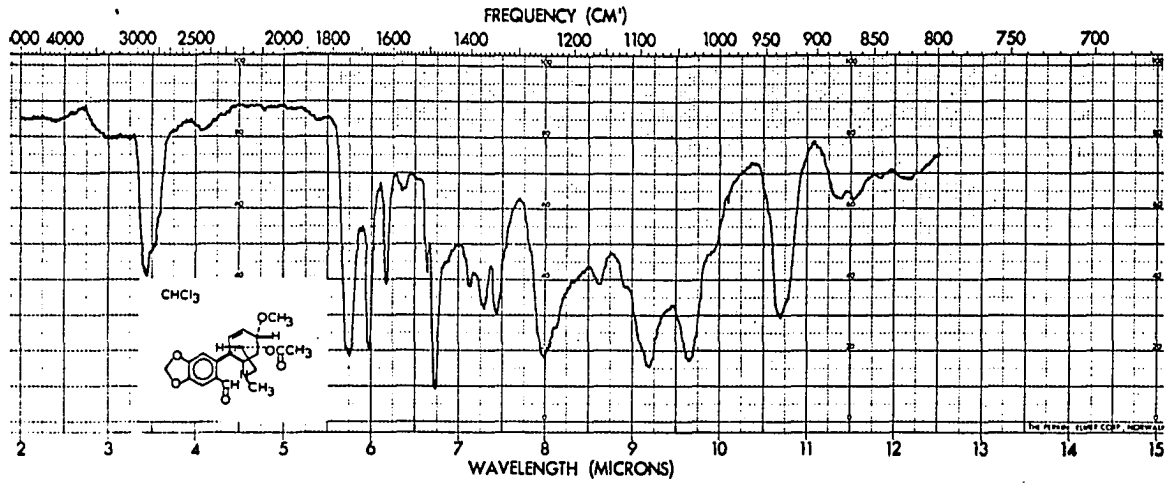
NONCRYSTALLINE PRODUCT ISOLATED FROM THIS REACTION HAD SOME OF THE PROPERTIES CHARACTERISTIC OF AN AROMATIC ALDEHYDE. THUS THE INFRARED SPECTRUM (FIG. 19A) OF 72 IN CHLOROFORM SHOWED ABSORPTION AT 5.75μ (ACETYL CARBONYL), 5.99μ (ALDEHYDE CARBONYL) AND 6.19μ (AROMATIC). THE ULTRAVIOLET SPECTRUM OF 72 IN CHLOROFORM SHOWED MAXIMA AT 315 AND 288 $m\mu$ WHICH IS CHARACTERISTIC OF AN UNSATURATED GROUPING IN CONJUGATION WITH AN AROMATIC RING. PURIFICATION OF THE ALDEHYDE (72) PRESENTED SOME SURPRISING PROBLEMS WHICH INDICATED THAT SOMETHING UNUSUAL WAS TAKING PLACE. THE COMPOUND WOULD NOT ELUTE FROM A CHROMATOGRAPHIC COLUMN (NEUTRAL ALUMINA OR FLORISIL) NOR WOULD IT MIGRATE ON THIN LAYER CHROMATOGRAPHIC PLATES. FURTHERMORE

FIG. 19: INFRARED SPECTRA

A: 11-ACETYL-N-METHYL-6-HYDROXY-
CRINAMINE (72)

B: HYDROXYLAMINE ADDUCT (73)

C: N-ACETYL HYDROXYLAMINE ADDUCT (74)



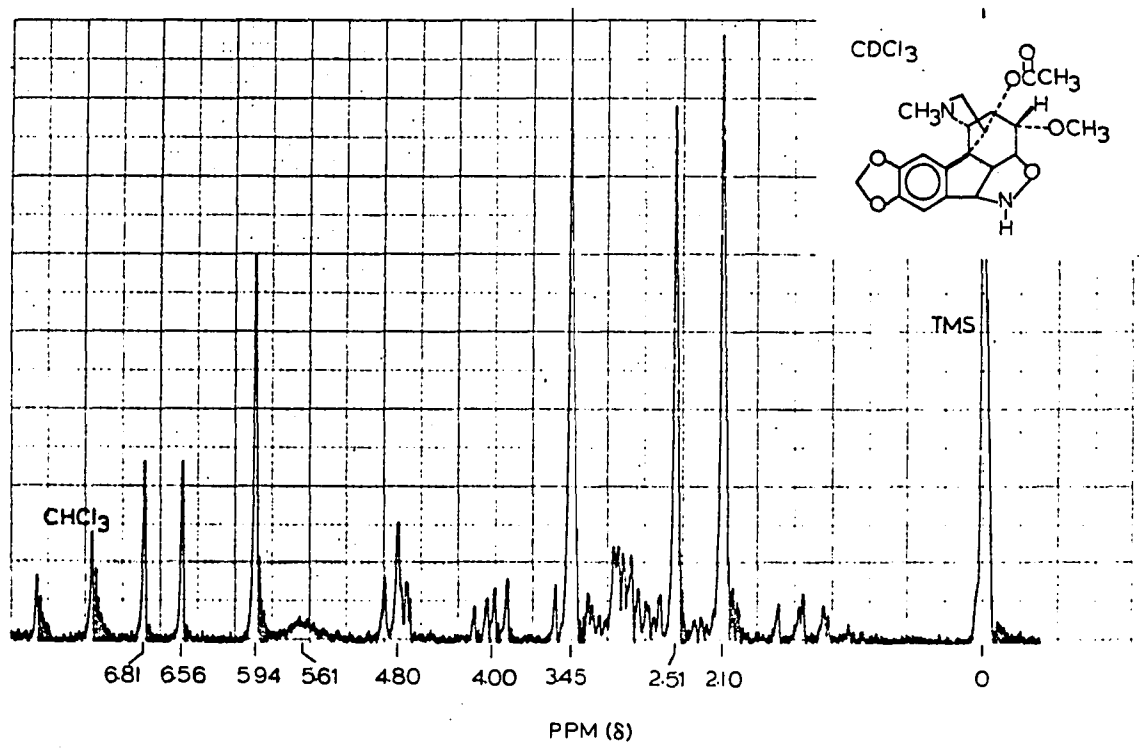
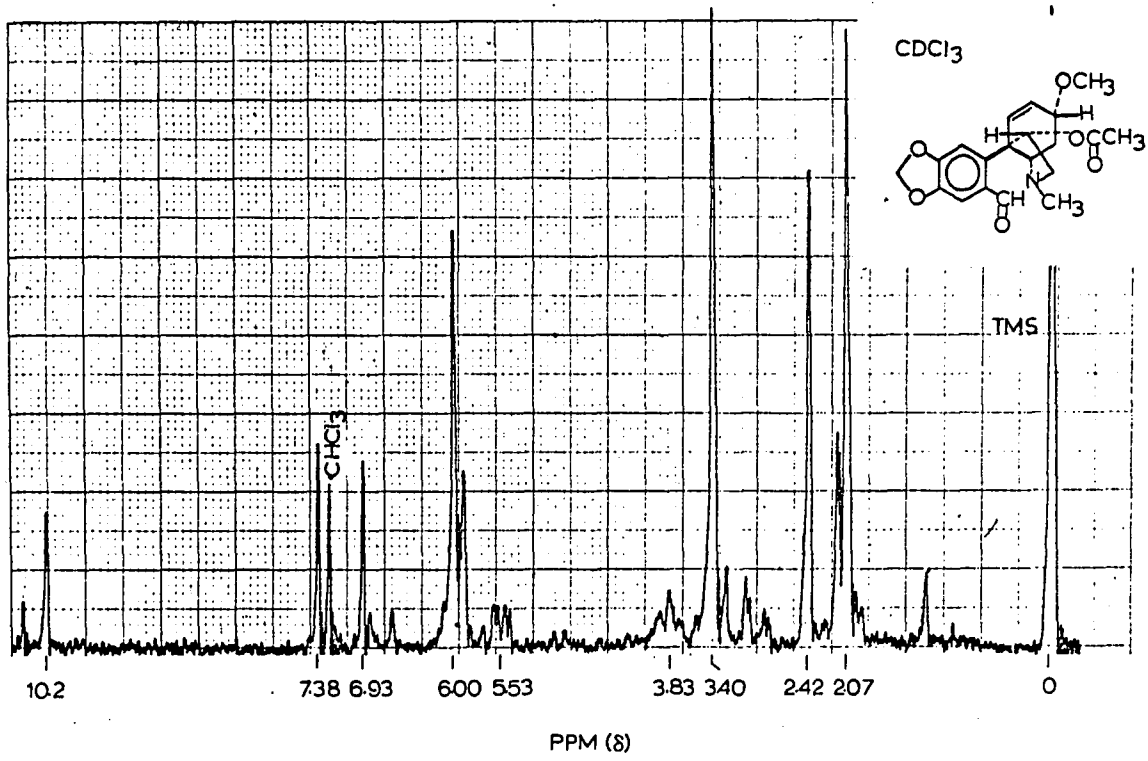
THE ULTRAVIOLET SPECTRUM OF 72 IN 95% ETHANOL SHOWED MAXIMA AT 290 AND 241 μ . THESE MAXIMA ARE IN ACCORD WITH A SIMPLE AROMATIC CHROMOPHORE. SINCE THE COMPOUND IS ALSO UNSTABLE ON A GAS PHASE CHROMATOGRAPH, THE ONLY ESTIMATE OF PURITY (ABOUT 90%) IS BASED UPON ITS N.M.R. SPECTRUM (FIG. 20A). THE PEAK AT 10.2 P.P.M. INDICATED THAT AN ALDEHYDE GROUP WAS INDEED PRESENT.^{41, p. 62} THIS SUPPOSITION IS SUPPORTED BY THE WIDELY SEPARATED AROMATIC PROTON PEAKS AT 7.38 AND 6.93 P.P.M. THE OLEFINIC AND METHYLENEDIOXY PROTONS PRODUCE PEAKS CENTERED AT 6.00 P.P.M. THE ROUGH QUARTET AT 5.53 P.P.M. MUST BE ASSIGNED TO THE C-11 PROTON ALTHOUGH IT IS AT LOWER FIELD THAN EXPECTED. THE TRIPLET AT 3.83 P.P.M. HAS A CHEMICAL SHIFT IN ACCORD WITH THAT EXPECTED FOR THE C-3 PROTON. THE METHOXYL, N-METHYL AND ACETYL PROTON SINGLETS APPEAR AT 3.40, 2.42 AND 2.07 P.P.M., RESPECTIVELY. ALTHOUGH THE N.M.R. SPECTRUM INDICATED THAT THE COMPOUND WAS NOT PURE, FURTHER PURIFICATION WAS NOT POSSIBLE BECAUSE OF THE REASONS MENTIONED ABOVE.

ONE OF THE EASIEST AND SIMPLEST WAYS TO CHARACTERIZE AN ALDEHYDE IS TO PREPARE AN OXIME DERIVATIVE. WITH THIS THOUGHT IN MIND, SOME OF THE ALDEHYDE 72 WAS HEATED WITH HYDROXYLAMINE HYDROCHLORIDE IN ETHANOL BUFFERED WITH SODIUM ACETATE. THE PRODUCT DID NOT HAVE THE EXPECTED OXIME CHARACTERISTICS. THE COMPOUND EASILY MIGRATES IN T.L.C. PLATES AND IS RECRYSTALLIZED FROM ETHYL ACETATE. THE INFRARED SPECTRUM (FIG. 19B) HAS ABSORPTION AT 5.75 μ (ACETYL CARBONYL) BUT NO C=N STRETCHING BAND. THE ULTRAVIOLET SPECTRUM CONFIRMED THIS SUSPICION

FIG. 20: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: 11-ACETYL-N-METHYL-6-HYDROXYCRINAMINE (72)

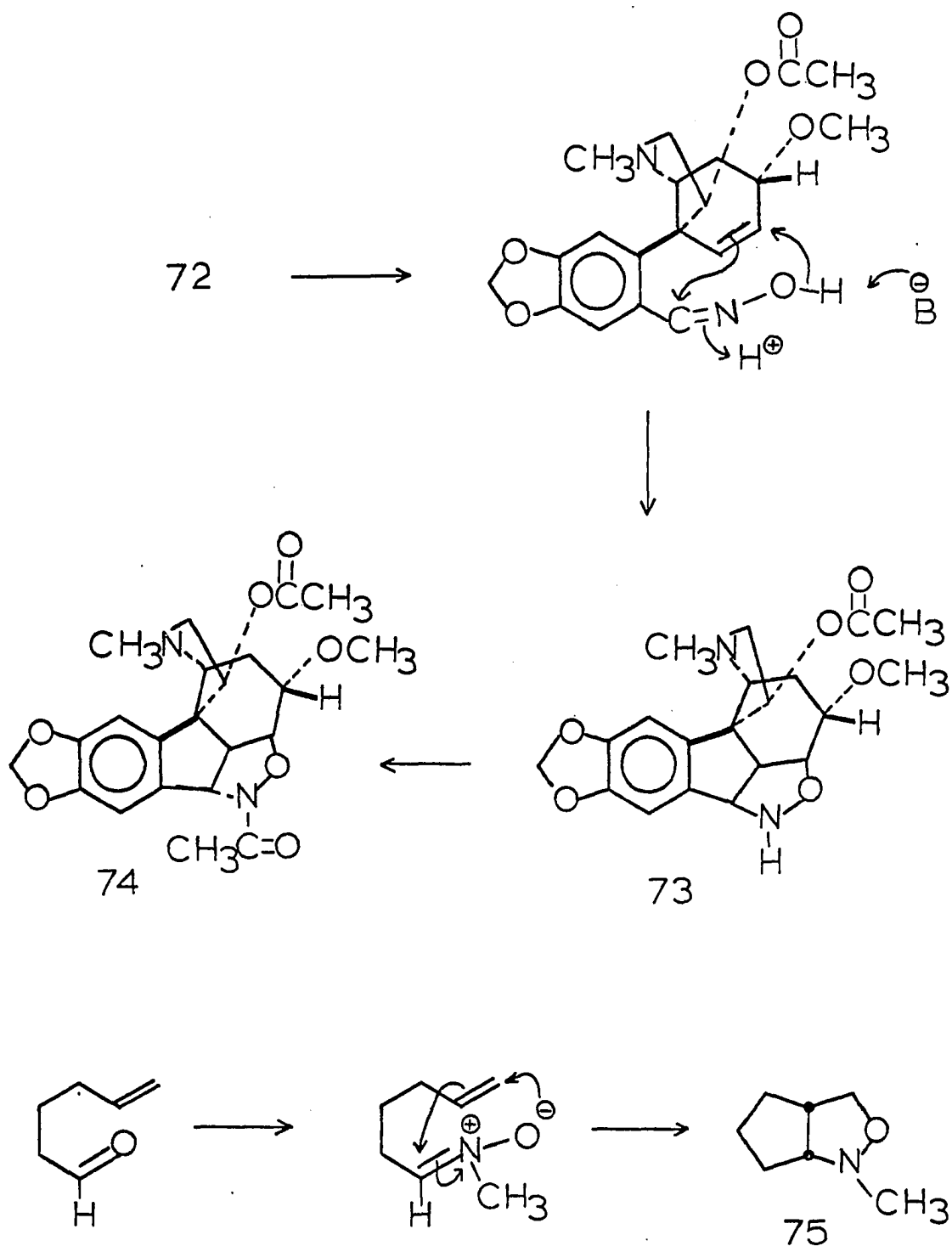
B: HYDROXYLAMINE ADDUCT (73)



BY EXHIBITING ABSORPTION AT 293 AND 236 μ , CHARACTERISTIC OF A METHYLENEDIOXY SUBSTITUTED BENZENE RING WITH NO BENZYLIC CONJUGATION. THE N.M.R. SPECTRUM (FIG. 20B) PROVIDED THE GREATEST SURPRISE WHEN IT SHOWED THE COMPLETE ABSENCE OF OLEFINIC PROTON PEAKS. THE AROMATIC PROTONS PRODUCED SINGLETS AT 6.81 AND 6.56 P.P.M. OF EQUAL INTENSITY, AND THE TWO PROTON SINGLET AT 5.94 P.P.M. MUST BE ASSIGNED TO THE METHYLENEDIOXY PROTONS. THE METHOXYL, N-METHYL AND ACETYL PROTONS ARE ASSIGNED TO THE THREE PROTON SINGLETS AT 3.45, 2.51 AND 2.10 P.P.M., RESPECTIVELY. THE BROAD ONE PROTON PEAK AT 5.61 P.P.M. WAS REMOVED UPON SHAKING THE SAMPLE WITH DEUTERIUM OXIDE WHICH INDICATED THIS PEAK TO BE A HYDROXYL OR AMINO PROTON. THE REST OF THE SPECTRUM CONSISTS OF SEVERAL WELL-DEFINED MULTIPLETS, SOME OF WHICH ARE IN THE 4 - 6 P.P.M. REGION. THE LATTER OBSERVATION SUGGESTS THAT AT LEAST THREE OF THE PROTONS MUST BE NEAR DESHIELDING GROUPS. THE ELEMENTAL ANALYSIS INDICATED THAT SINCE THE COMPOUND HAS THE SAME EMPIRICAL FORMULA ($C_{20}H_{24}N_2O_6$) AS THE EXPECTED OXIME DERIVATIVE, THE TOTAL AMOUNT OF UNSATURATION REMAINS THE SAME. THE FACT THAT THERE ARE NO OLEFINIC PROTONS IN THE N.M.R. SPECTRA AND NO BENZYLIC UNSATURATION IN THE PRODUCT INDICATES THAT TWO NEW RINGS, TWO TETRASUBSTITUTED DOUBLE BONDS OR ONE OF EACH MUST HAVE BEEN CREATED IN THE REACTION. THE SAME COMPOUND WAS PREPARED BY HEATING THE ALDEHYDE 72 WITH HYDROXYLAMINE HYDROCHLORIDE IN PYRIDINE. THIS RESULT INDICATED THAT THE REACTION IS SOLVENT INDEPENDENT AND MAY BE INTRAMOLECULAR IN NATURE.

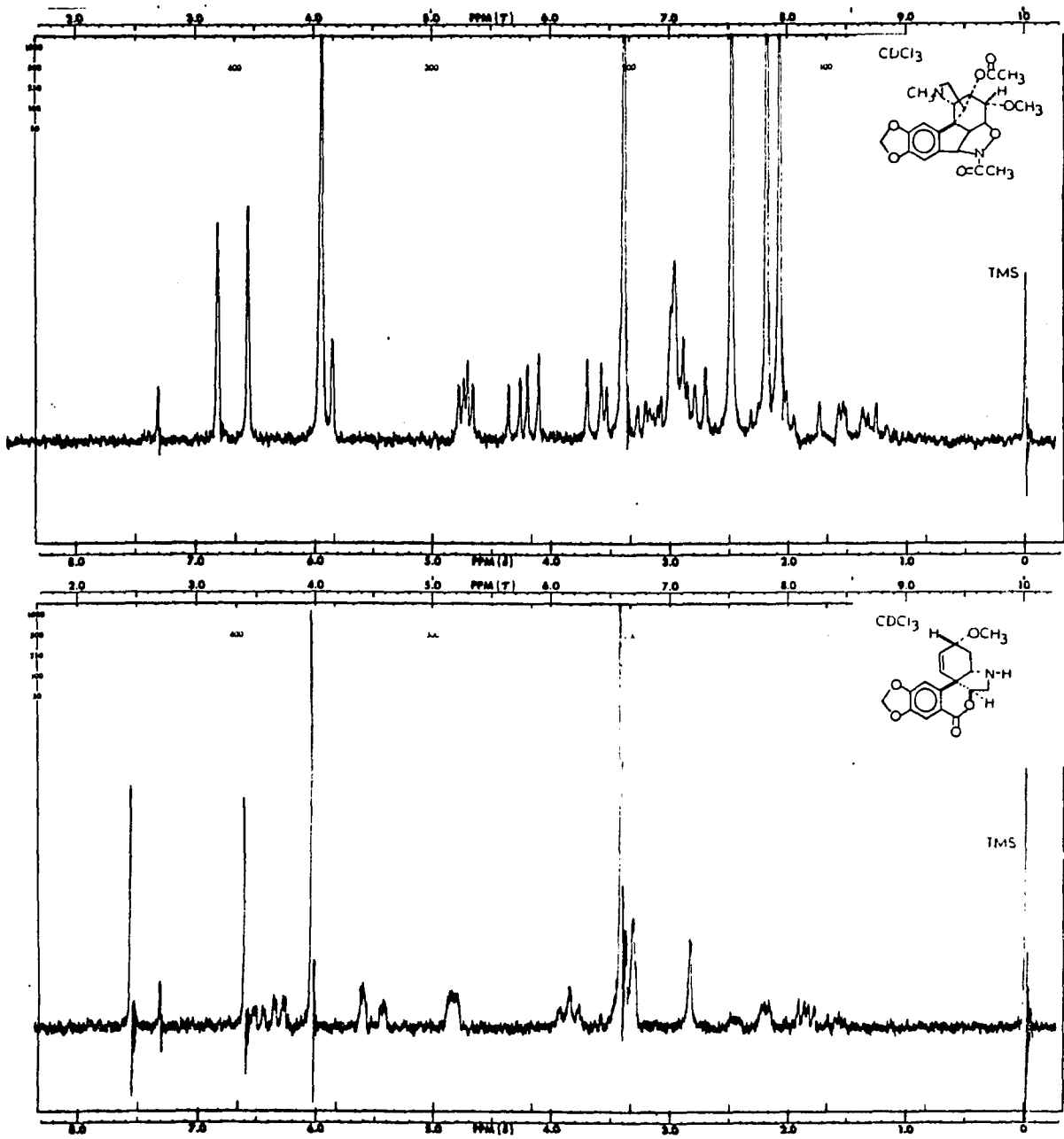
THE KEY TO THE STRUCTURE OF THE HYDROXYLAMINE PRODUCT WAS FOUND IN ITS CONVERSION TO ITS N-ACETYL DERIVATIVE. THE INFRARED SPECTRUM OF THE AMIDE (FIG. 19C) SHOWED ABSORPTION AT 5.75μ (O-ACETYL CARBONYL) AND 6.02μ (N-ACETYL CARBONYL). THE ULTRAVIOLET SPECTRUM INDICATED THAT NO NEW CONJUGATION WAS CREATED AND ABSORPTION WAS FOUND AT 292 AND 235 $m\mu$. THE N.M.R. SPECTRUM OF THE AMIDE IS PRESENTED IN FIG. 21A. THE AROMATIC PROTONS PRODUCE RESONANCES AT 6.55 AND 6.70 P.P.M. THE METHYLENEDIOXY PROTON SINGLET AT 5.95 P.P.M. IS SUPERIMPOSED UPON A ONE PROTON DOUBLET, ONE OF WHOSE PEAKS CAN BE SEEN AT 5.84 P.P.M. THE PEAKS AT 4.7 P.P.M. HAVE A CHEMICAL SHIFT EXPECTED FOR THE PROTON ON THE O-ACETYL BEARING CARBON. THE THREE PROTON SINGLETS AT 3.39, 2.58, 2.19 AND 2.08 P.P.M. ARE TENTATIVELY ASSIGNED TO THE METHOXYL, N-METHYL, N-ACETYL AND O-ACETYL PROTONS, RESPECTIVELY. AGAIN ONE PROTON MULTIPLETS AT 5.9, 4.2 AND 3.6 P.P.M. SUGGEST THAT THE PROTONS PRODUCING THESE PEAKS ARE ADJACENT TO ELECTRONEGATIVE ATOMS OR DESHIELDING GROUPS.

AFTER A GREAT DEAL OF CONSIDERATION, THE ISOXAZOLIDINE COMPOUNDS 73 AND 74 ARE PROPOSED FOR THE HYDROXYLAMINE ADDUCT AND ITS ACETYLATED DERIVATIVE. THE PRECEDENT FOR THIS REACTION ORIGINATES WITH THE REACTION OF N-METHYLHYDROXYLAMINE AND 5-HEXANAL TO GIVE THE ISOXAZOLIDINE 75.⁵³ THE MECHANISM OF CYCLIZATION IS EQUALLY APPLICABLE TO THE OXIME DERIVATIVE OF 72 AND IS FAVORED BY THE PROXIMITY OF THE RING C DOUBLE BOND TO THE OXIME. THE N.M.R. SPECTRUM OF 74 IS CONSISTENT WITH

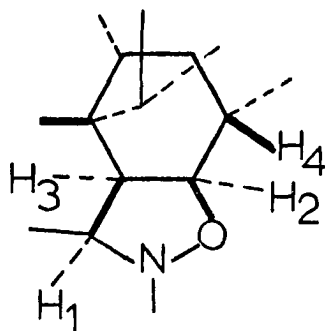


THIS STRUCTURE AND VARIOUS PROTON COUPLINGS CAN TENTATIVELY BE ASSIGNED. ON THE BASIS OF CHEMICAL SHIFTS, THE MULTIPLETS AT 5.9, 4.2 AND 3.6 P.P.M. MAY BE ASSIGNED TO H₁, H₂ AND H₃, RE-

FIG. 21: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: N-ACETYL HYDROXYLAMINE ADDUCT (74)
B: 6A-EPI-N-DEMETHYLMACRONINE (82)

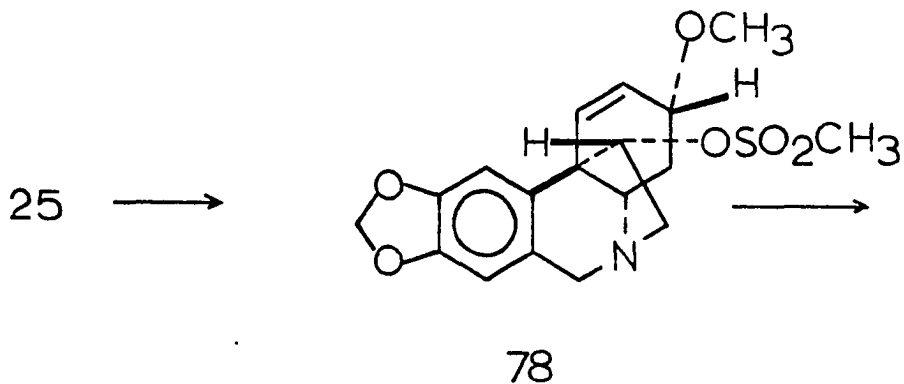


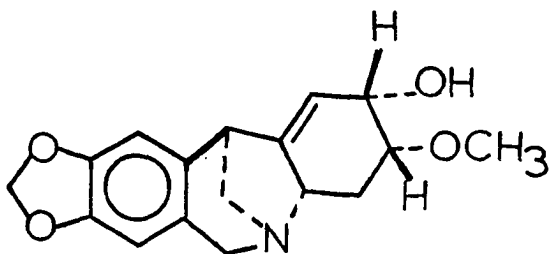
SPECTIVELY. H_1 IS COUPLED TO H_3 ($J = 7.0$ C.P.S.) AND H_3 IS COUPLED TO H_2 ($J = 9.8$ C.P.S.). H_2 IN TURN IS COUPLED TO H_4 ($J = 5.0$ C.P.S.) WHOSE RESONANCE IS OBSCURED IN THE 3 P.P.M. REGION. THE STRUCTURES OF 73 AND 74 MUST BE REGARDED AS TENTATIVE UNTIL FURTHER EVIDENCE IS OBTAINED.



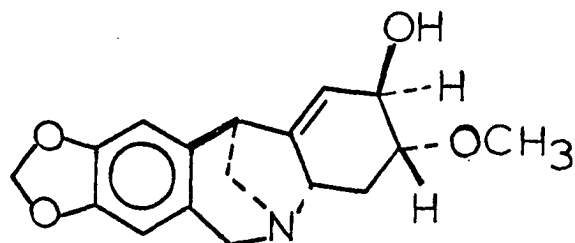
ATTEMPTED REARRANGEMENT OF 6-OXOCRINAMINE TO 6-OXOISOCRINAMINE

CRINAMINE (25) HAS BEEN SHOWN TO UNDERGO REARRANGEMENT TO α AND β ISOCRINAMINE (76 AND 77, RESPECTIVELY) VIA THE MESYLATE 78.⁵⁴ A SIMILAR REARRANGEMENT OF 6-OXOCRINAMINE (37) WOULD GIVE THE NOVEL BRIDGEHEAD LACTAM 79. REDUCTION OF 79 WITH LITHIUM ALUMINUM HYDRIDE WOULD GIVE 6-HYDROXYISOCRINAMINE WHOSE PROPERTIES COULD BE COMPARED WITH THOSE OF 6-HYDROXY-



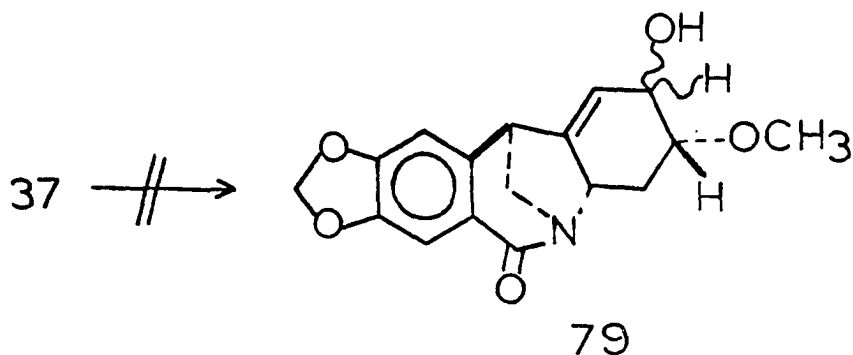


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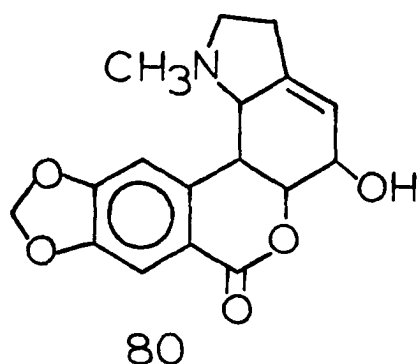


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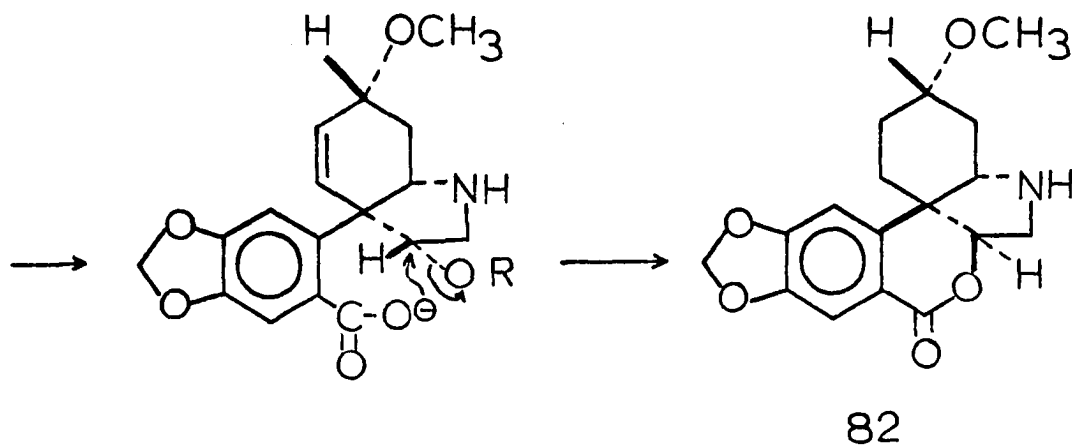
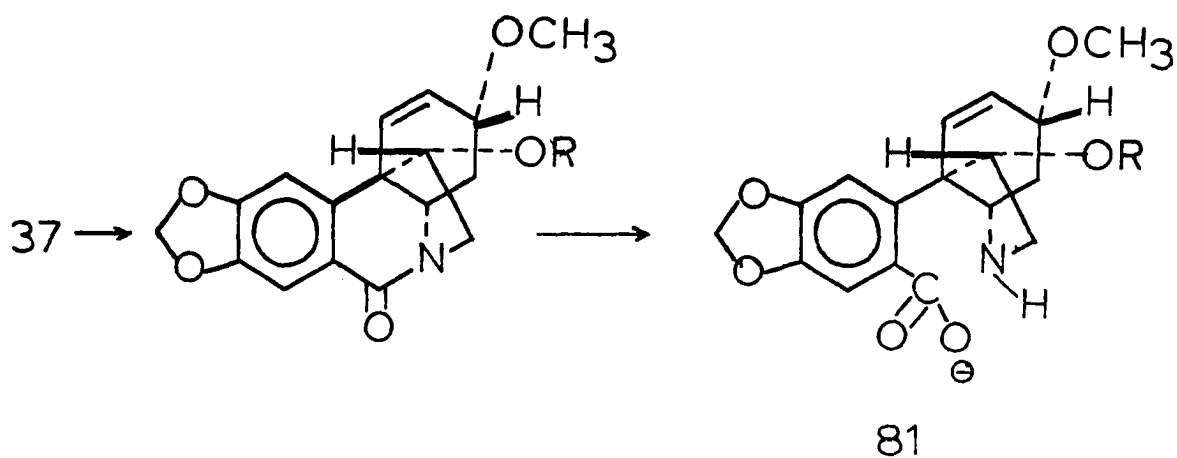
CRINAMINE. IN ACCORD WITH THE ORIGINAL PROCEDURE,⁵⁴ 6-OXO-CRINAMINE WAS DISSOLVED IN PYRIDINE AND METHANESULFONYL CHLORIDE WAS ADDED. THE MESYLATE WAS DECANTED INTO A BICARBONATE SOLUTION AND THE HYDROLYZED PRODUCT ISOLATED. THE PRODUCT WAS PURE BY T.L.C. AND SHOWED ABSORPTION IN THE INFRARED (FIG. 6B) AT 5.88 AND 6.18 μ . THE N.M.R. SPECTRUM (FIG. 21B) INDICATED THAT ALTHOUGH THE REACTION PRODUCT WAS NOT THE STARTING MATERIAL, IT ALSO WAS NOT THE DESIRED PRODUCT. THIS CONCLUSION IS BASED UPON THE FACT THAT THERE ARE TWO OLEFINIC PROTON PEAKS IN THE N.M.R. SPECTRUM WHEREAS THE ISOCRINAMINE STRUCTURES



HAVE ONE OLEFINIC PROTON. THE AROMATIC PROTON ADJACENT TO THE CARBONYL GROUP APPEARS IN THE N.M.R. SPECTRUM AT 7.56 P.P.M. AND THE REMAINING AROMATIC PROTON GIVES RISE TO A SINGLET AT 6.60 P.P.M. THE OLEFINIC PROTONS GIVE PEAKS THAT FORM THE AB PART OF AN ABX PATTERN. THE METHYLENEDIOXY PROTONS PRODUCE A SINGLET AT 6.04 P.P.M. AND THE ONE PROTON MULTIPLY AT 4.8 P.P.M. IS APPARENTLY PRODUCED BY A PROTON ADJACENT TO AN ELECTRONEGATIVE ATOM. THE TRIPLY AT 3.8 P.P.M. IS TENTATIVELY ASSIGNED TO THE PROTON ATTACHED TO THE METHOXYL BEARING CARBON. THE METHOXYL PROTONS GIVE RISE TO A SINGLET AT 3.42 P.P.M. AND THE SINGLET AT 2.85 P.P.M. MAY BE THE RESONANCE OF EITHER AN AMINO OR HYDROXYL PROTON. THE ULTRAVIOLET ABSORPTION OF THE REARRANGED PRODUCT (MAXIMA AT 230, 267 AND 308 $m\mu$) HAS SHIFTED FROM THAT OF 6-OXOCRINAMINE (MAXIMA AT 234, 274 AND 315 $m\mu$) AND CLOSELY RESEMBLES THAT OF HIPPEASTRINE (80) (MAXIMA AT 227, 268 AND 308 $m\mu$). THIS OBSERVATION LED TO THE CONCLUSION THAT THE REACTION PRODUCT MAY BE A LACTONE AND NOT A LACTAM. THIS POSTULATION IS REASONABLE BECAUSE IF UPON BASIC HYDROLYSIS THE



CARBOXYLATE ANION 81 IS FORMED, IT COULD DISPLACE THE MESYLATE GROUP TO GIVE THE LACTONE 82. THE N.M.R. SPECTRUM IS IN ACCORD WITH THIS STRUCTURE AND THE 6A PROTON WOULD GIVE RISE TO THE PEAKS AT 4.8 P.P.M. FURTHER EVIDENCE SUPPORTING THE STRUCTURE 82 WILL BE PRESENTED IN THE SECTION ON THE STRUCTURE PROOF OF MACRONINE.



MASS SPECTRA OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE

A DISCUSSION OF THE MASS SPECTRAL FRAGMENTATION OF SEVERAL AMARYLLIDACEAE ALKALOIDS HAS BEEN PUBLISHED IN CONJUNCTION WITH PROFESSOR CARL DJERASSI AND COWORKERS OF STANFORD UNIVERSITY.⁵⁵ TO AVOID UNNECESSARY AND UNINFORMATIVE DUPLICATION, ONLY THE MASS SPECTRA OF ALKALOIDS RELATED TO 6-HYDROXYCRINAMINE WILL BE PRESENTED AND DISCUSSED IN THIS THESIS. SINCE THE ABOVE PAPER ON THE FRAGMENTATION OF AMARYLLIDACEAE ALKALOIDS APPEARED, MORE STUDIES HAVE BEEN COMPLETED AND ARE PRESENTED IN ADDITION TO SOME OF THE PUBLISHED WORK.

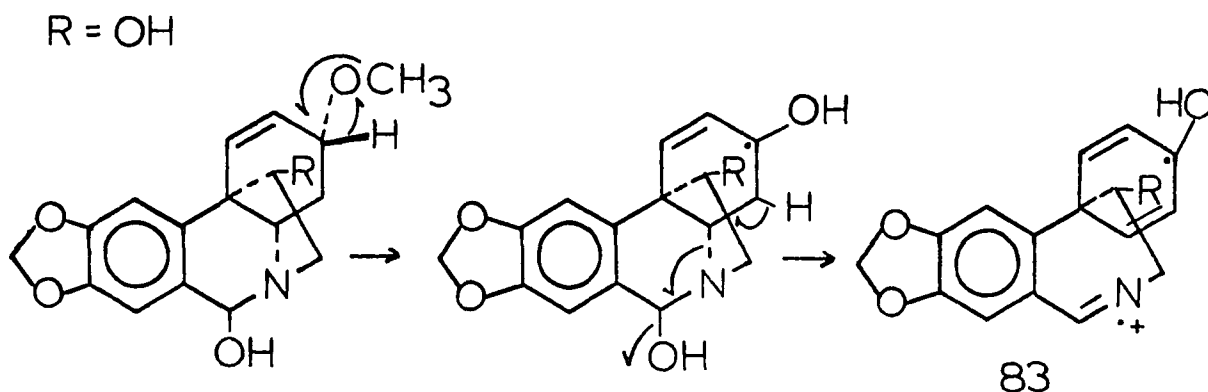
TWO USEFUL TECHNIQUES USED TO FACILITATE THE ASSIGNMENT OF STRUCTURES TO MASS SPECTRAL FRAGMENTS ARE HIGH RESOLUTION MASS SPECTROMETRY⁵⁶ AND ISOTOPE LABELING. THE MERITS OF HIGH RESOLUTION MASS SPECTROMETRY CAN BE REALIZED WHEN SEVERAL IONS OF DIFFERENT EMPIRICAL FORMULAS GIVE RISE TO THE SAME MASS PEAK. THESE IONS CAN BE RESOLVED INTO THEIR COMPONENT PEAKS AND THEIR EXACT MOLECULAR WEIGHT OBTAINED BY THIS METHOD. HIGH RESOLUTION MASS SPECTRAL DATA IS ESPECIALLY USEFUL IN STUDYING THE COMPLEX FRAGMENTS PRODUCED UPON THE ELECTRON BOMBARDMENT OF ALKALOIDS.

ISOTOPE LABELING ALSO ENABLES ONE TO DECIDE BETWEEN ALTERNATIVE FRAGMENT STRUCTURES. THE INTRODUCTION OF ONE ATOM OF ONE GREATER MASS THAN THE ORIGINAL MASS IS SEEN AS A SHIFT OF ONE MASS UNIT IN ALL FRAGMENTS CONTAINING THAT ATOM. THE GREATEST PROBLEM WITH ISOTOPE LABELING LIES IN THE INTRODUCTION OF THE ISOTOPE INTO THE MOLECULE. DEUTERIUM, HOWEVER,

CAN USUALLY BE INTRODUCED INTO AN ORGANIC COMPOUND BY ONE OF SEVERAL METHODS.⁴, CHAPT. 2 CONSEQUENTLY, MOST LABELING IS CARRIED OUT WITH DEUTERIUM AND THIS WAS THE METHOD OF CHOICE WITH THE AMARYLLIDACEAE ALKALOIDS STUDIED.

COMPLETE DESCRIPTIONS OF LABELING TECHNIQUES, MASS SPECTRAL TECHNIQUES, HIGH RESOLUTION METHODS AND PROBABLE MASS SPECTRAL FRAGMENTATION MECHANISMS ARE PRESENTED IN BOOKS BY BUDZIKIEWICZ, WILLIAMS AND DJERASSI,⁴ BEYNON,⁵⁶ BIEMANN⁵⁷ AND MCLAFFERTY.⁵⁸

THE MASS SPECTRUM OF 6-HYDROXYCRINAMINE (FIG. 22A) EXHIBITS A BASE PEAK AT M/E 268 BUT ALMOST NO PARENT ION PEAK AT M/E 317. THE LARGE ION PEAK AT M/E 284 (M - 33) ARISES AS THE RESULT OF THE LOSS OF A METHYL RADICAL PLUS WATER, POSSIBLY TO GIVE ION 83. THE LOSS OF A HYDROXYL RADICAL FROM THE M - 32

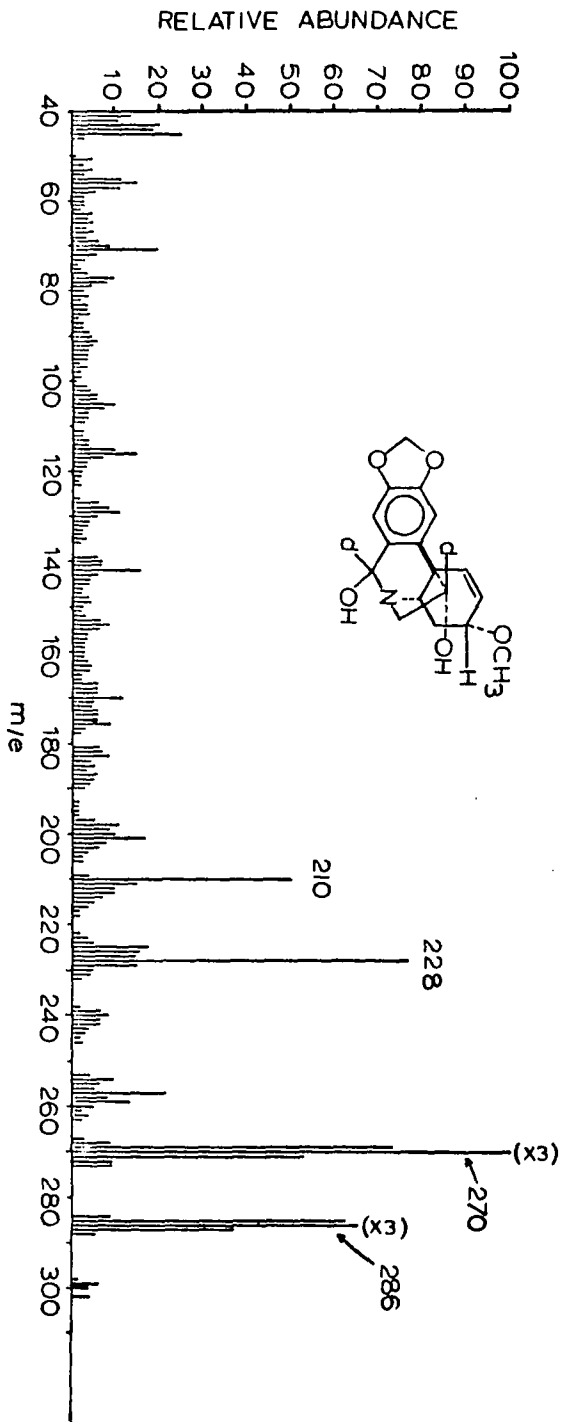
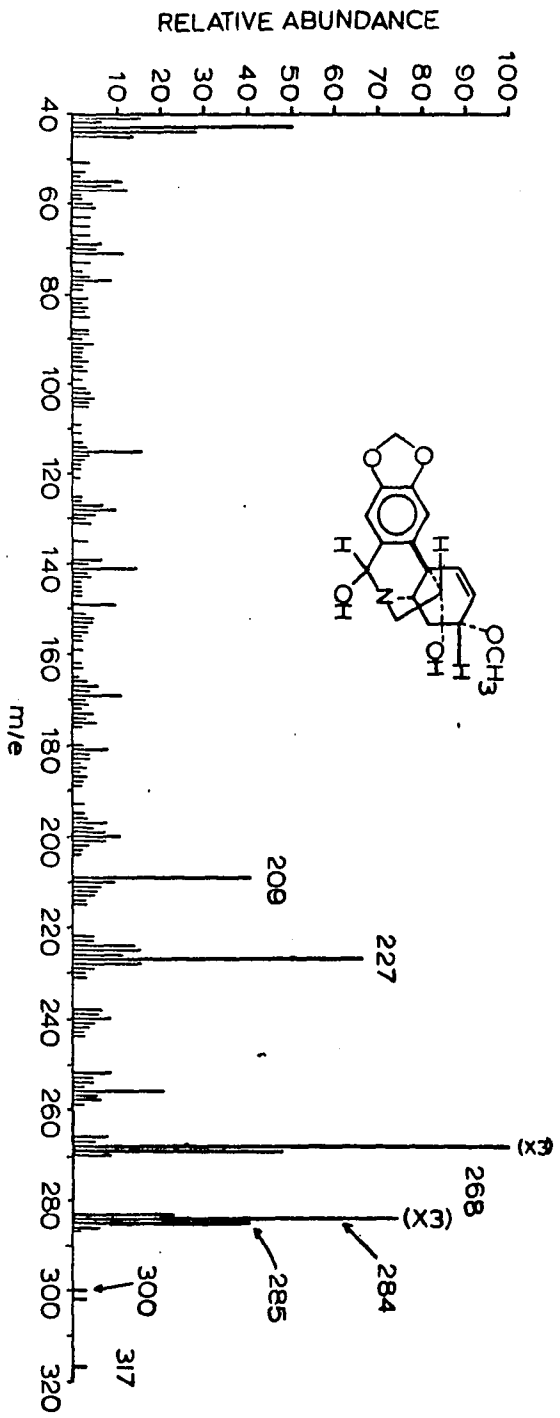


PEAK (M/E 285)(84) WOULD GIVE THE STABLE ION 85 AS THE BASE PEAK FRAGMENT AT M/E 268. A SIMILAR LOSS OF METHANOL IS NOTED IN THE MASS SPECTRA OF CRINAMINE AND HAEMANTHAMINE.⁵⁵ TWO SMALL PEAKS AT M/E 302 AND M/E 300 INDICATE THAT THE LOSS OF A METHYL RADICAL OR A HYDROXYL RADICAL ARE EITHER NOT FAVOR-

FIG. 22: MASS SPECTRA

A: 6-HYDROXYCRINAMINE (35)

B: 6-HYDROXYCRINAMINE-6,11-D₂ (56)



THE MASS SPECTRUM OF 6-HYDROXYCRINAMINE-6,11-D₂ (FIG. 22B) SUPPORTS THE ABOVE ASSIGNMENTS. FRAGMENTS 83 AND 85 SHOW AN INCREASE OF TWO MASS UNITS WHEREAS THE IONS 87 AND 88 ARE SHIFTED BY ONE MASS UNIT.

THE MASS SPECTRUM OF HAEMANTHIDINE (FIG. 23A) IS SIMILAR TO THAT OF 6-HYDROXYCRINAMINE BUT IT IS EVIDENT THAT THE CONFIGURATION OF THE METHOXYL GROUP PLAYS AN IMPORTANT ROLE IN THE FRAGMENTATION. A NOTICEABLE DIFFERENCE IN THE TWO SPECTRA IS THE LARGE PARENT ION PEAK (M/E 317) IN THE SPECTRUM OF HAEMANTHIDINE. THE BASE PEAK IN THE SPECTRUM OF HAEMANTHIDINE (M/E 227) INDICATES THAT α CLEAVAGE IS A MORE IMPORTANT PROCESS AND THAT IT OCCURRED BEFORE THE LOSS OF METHANOL, OTHERWISE A SIMILAR INTENSE PEAK WOULD BE FOUND AT M/E 268 AS IN THE SPECTRUM OF 6-HYDROXYCRINAMINE.

APOHAEMANTHIDINE (22) UPON ELECTRON BOMBARDMENT GIVES RISE TO THE SPECTRUM SHOWN IN FIG. 23B. THE BASE PEAK IN THE SPECTRUM IS THE MOLECULAR ION (M/E 285). LOSS OF WATER GIVES THE ION 89 (M/E 267). THE LARGE PEAK AT M/E 230 PROBABLY ARIS-

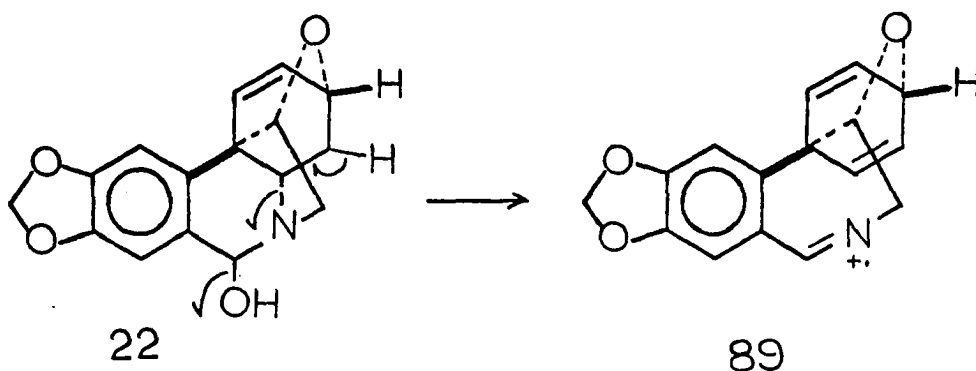
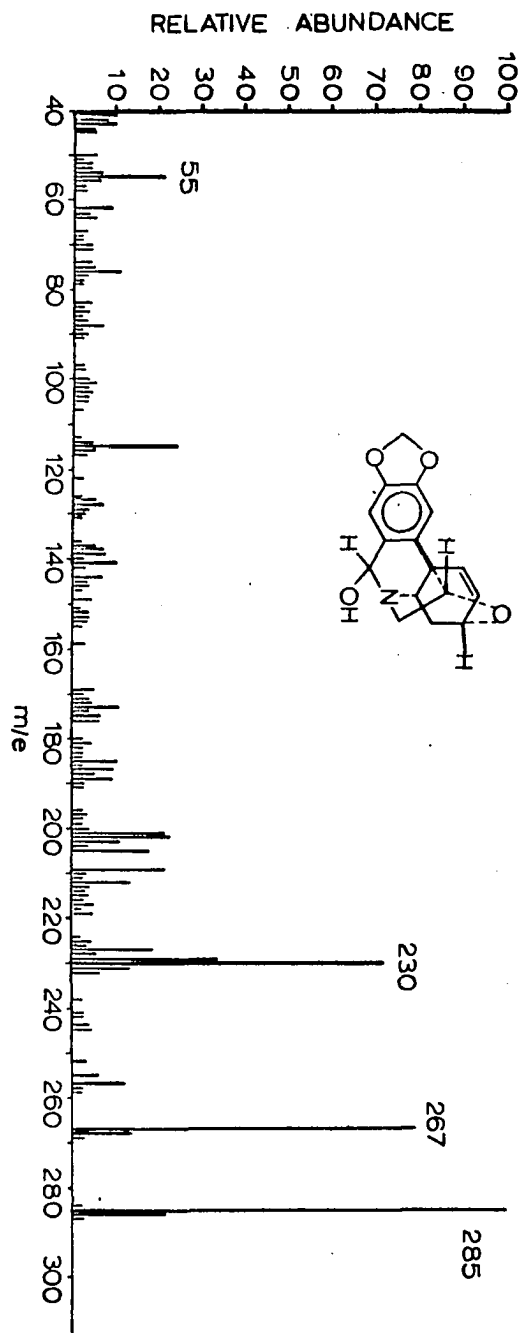
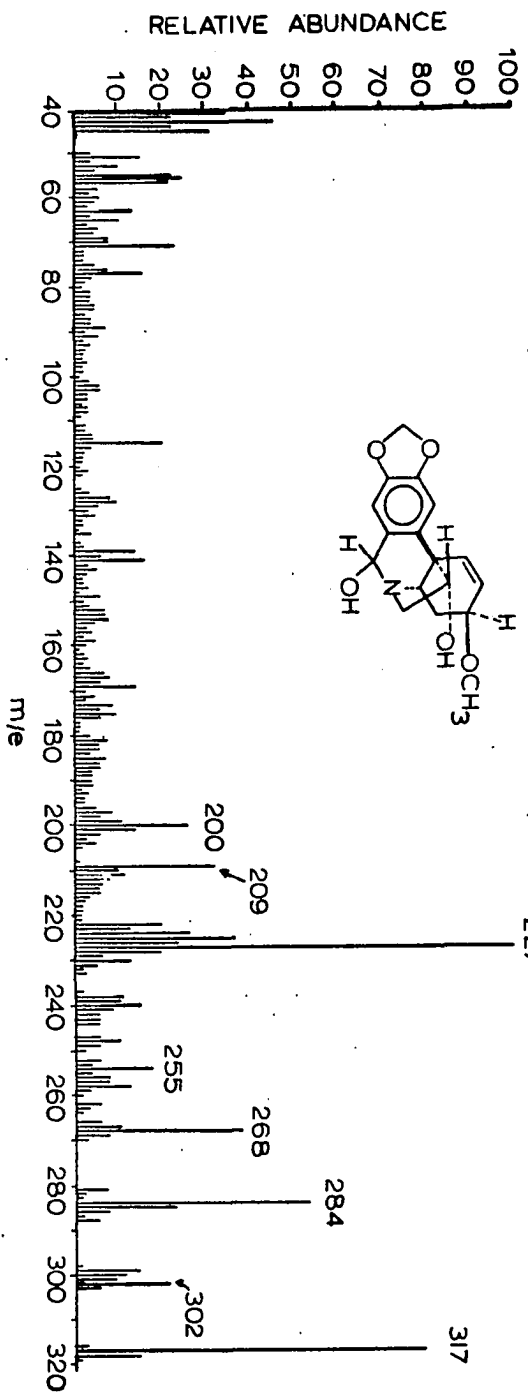


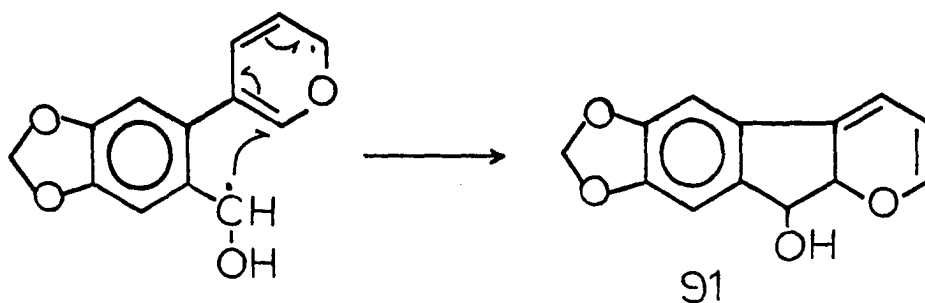
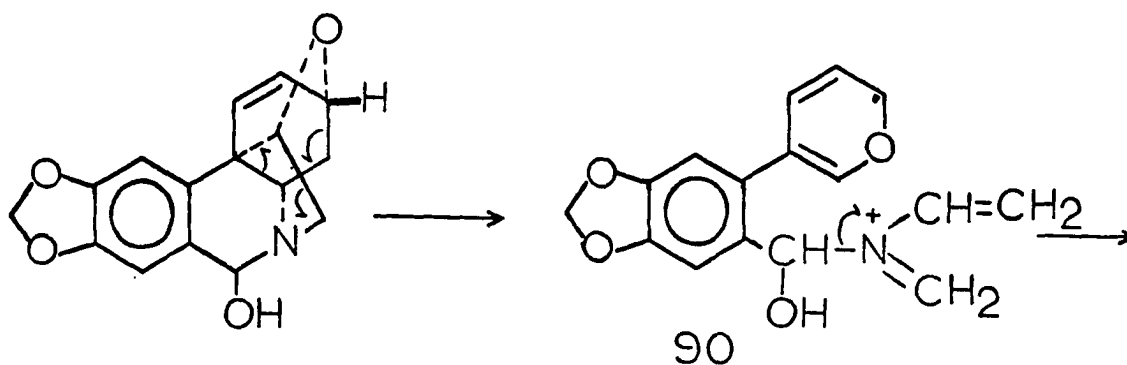
FIG. 23: MASS SPECTRA

A: HAEMANTHIDINE (32)

B: APOHAEMANTHIDINE (22)



ES DIRECTLY FROM THE FRAGMENTATION OF THE PARENT ION. CLEAVAGE α TO THE ETHER GIVES THE INTERMEDIATE 90 WHICH UNDERGOES THE LOSS OF $\text{CH}_2=\text{CHN}-\text{CH}_2$ (M/E 55) TO GIVE THE ION 91 (M/E 230). NO LABELED APOHAEMANTHIDINE HAS BEEN PREPARED TO SUPPORT THE ABOVE POSTULATED FRAGMENTATIONS.



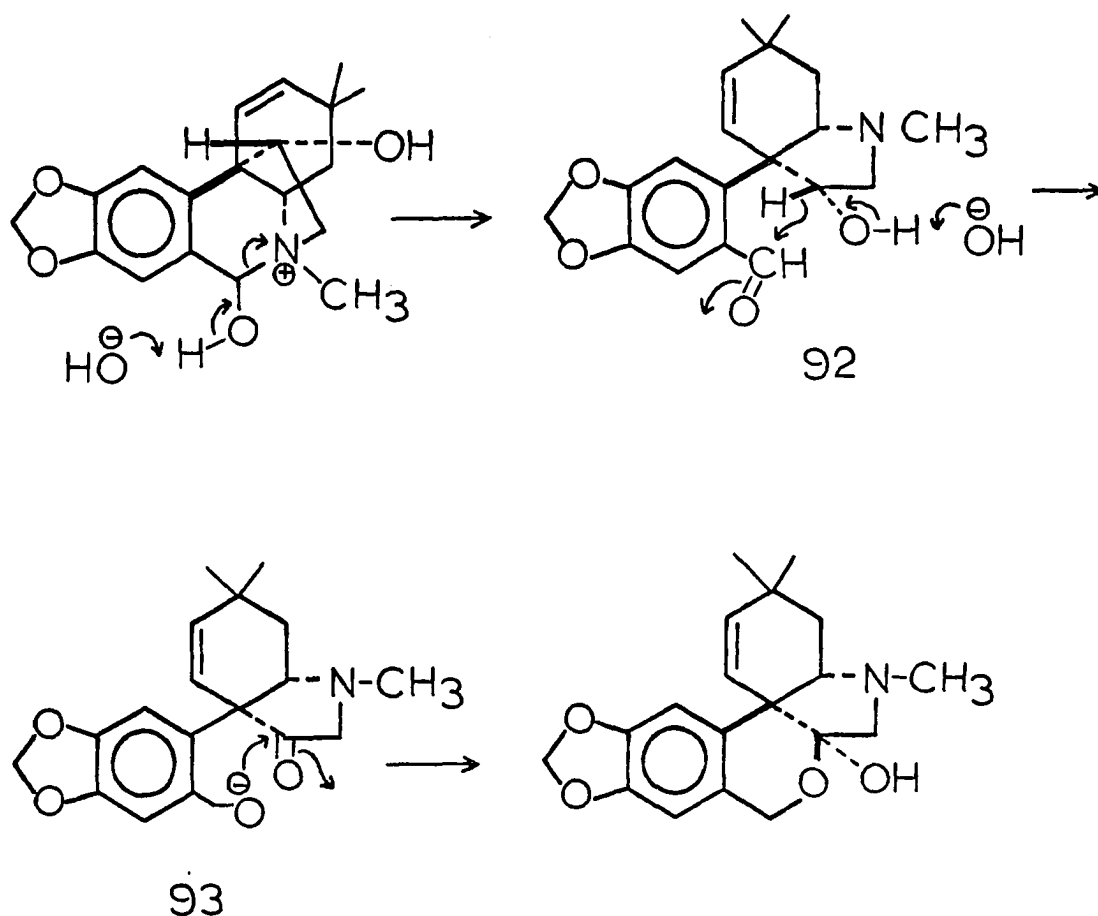
CRIWELLINE AND TAZETTINE

THE REARRANGEMENT OF 6-HYDROXYCRINAMINE TO CRIWELLINE

ALTHOUGH THE CONVERSION OF 6-HYDROXYCRINAMINE TO CRIWELLINE AND THE CORRESPONDING CONVERSION OF HAEMANTHIDINE TO TAZETTINE HAVE BEEN KNOWN FOR SOME TIME,^{24, 16} THE MECHANISMS OF

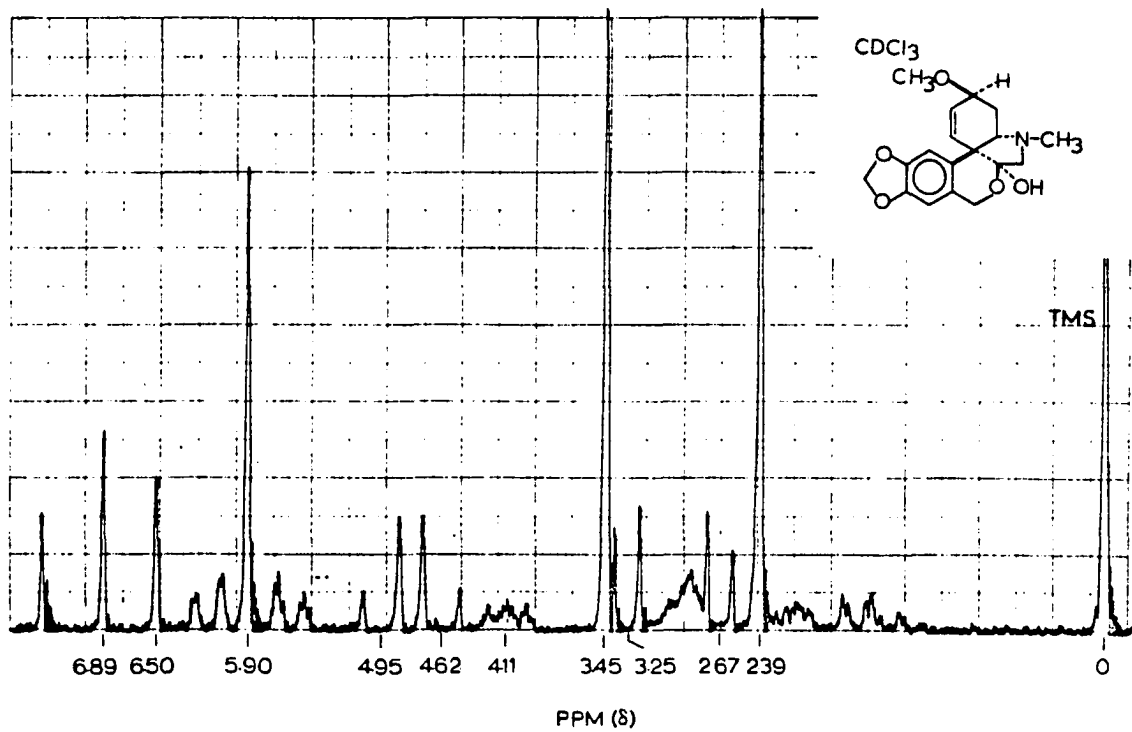
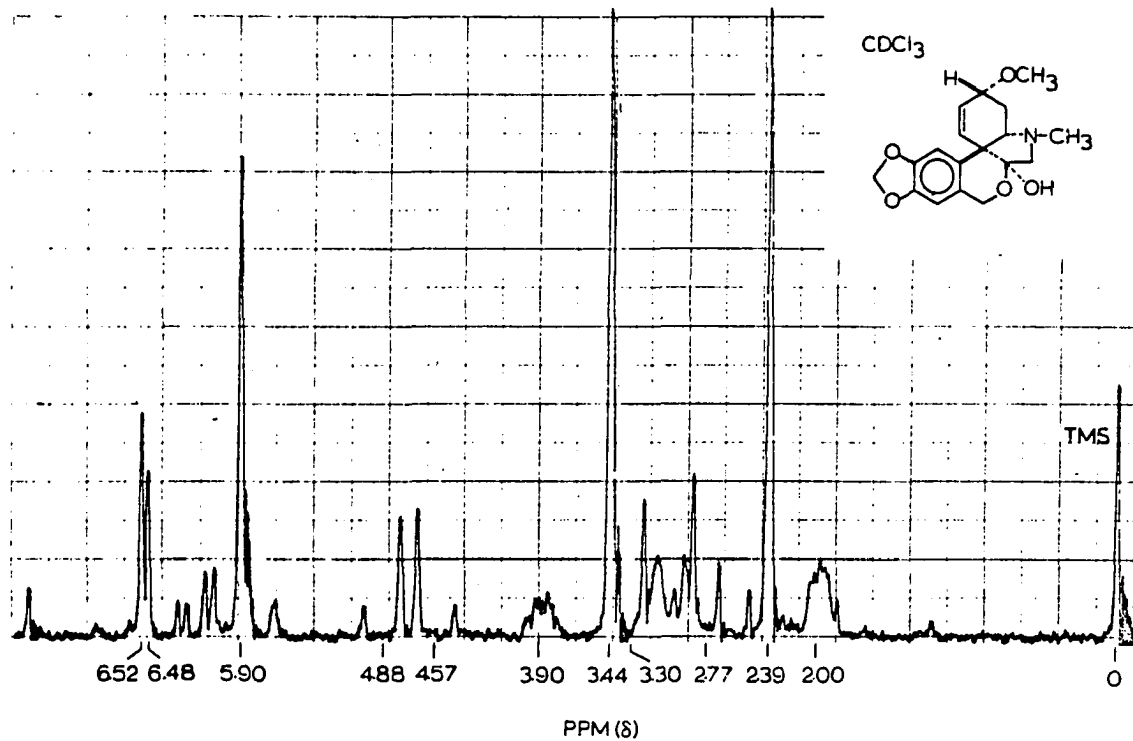
THESE REARRANGEMENTS ARE NOT KNOWN. A POSSIBLE MECHANISM HAS BEEN PRESENTED BY WILDMAN¹, P. 373 AND WARNHOFF,², P. 941

THESE PROPOSALS SUGGEST THAT BASE REACTS WITH THE CORRESPONDING METHIODIDE TO GIVE THE ALDEHYDE 92. THE KEY STEP IN THE REARRANGEMENTS IS THE BASE CATALYZED HYDRIDE TRANSFER TO GIVE KETO ALCOHOL 93. SUBSEQUENT CYCLIZATION GIVES THE HEMIKETAL (CRIWELLINE OR TAZETTINE).



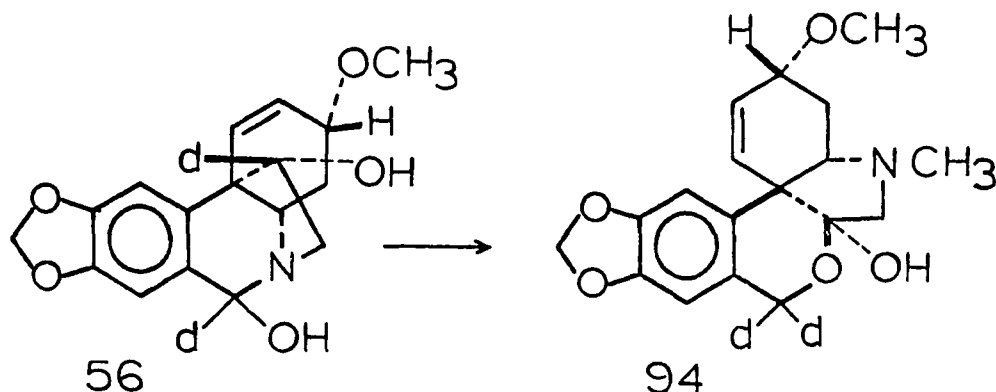
THE N.M.R. SPECTRUM OF CRIWELLINE (FIG. 24A) INDICATED THAT THE MECHANISM OF THE 6-HYDROXYCRINAMINE-CRIWELLINE CONVERSION COULD BE STUDIED BY DEUTERIUM LABELING. THE N.M.R. SPECTRA OF CRIWELLINE AND TAZETTINE HAVE BEEN DISCUSSED ELSE-

FIG. 24: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: CRIWELLINE (36)
B: TAZETTINE (20)



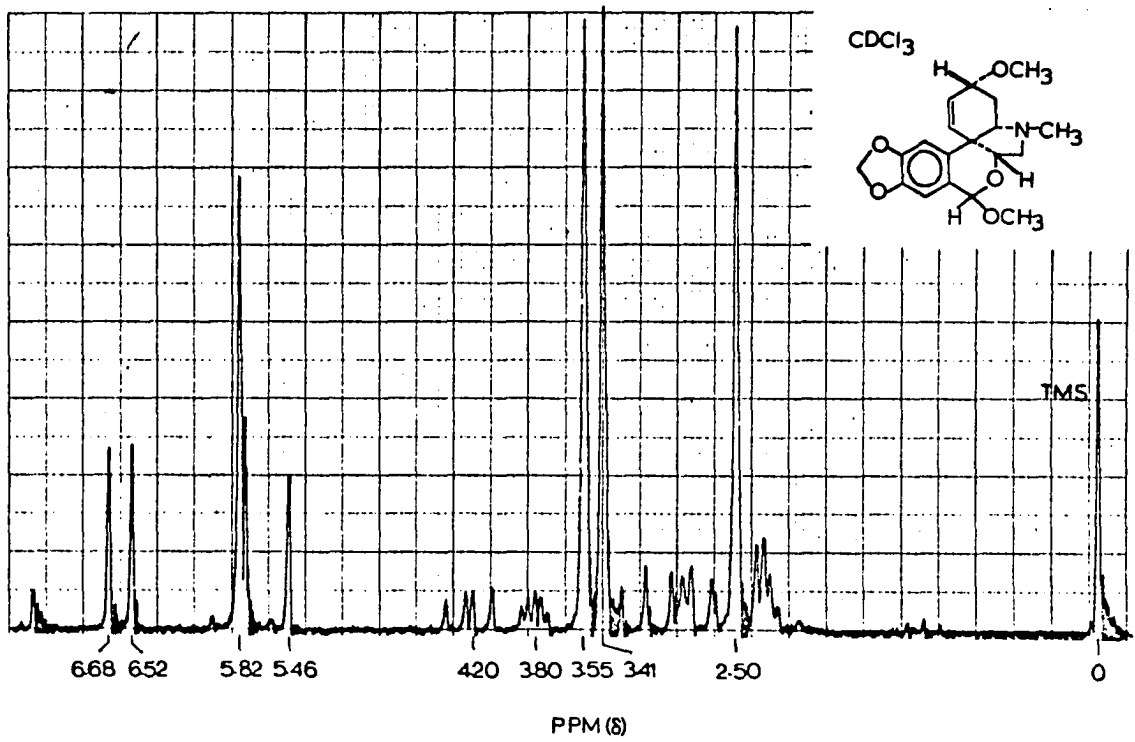
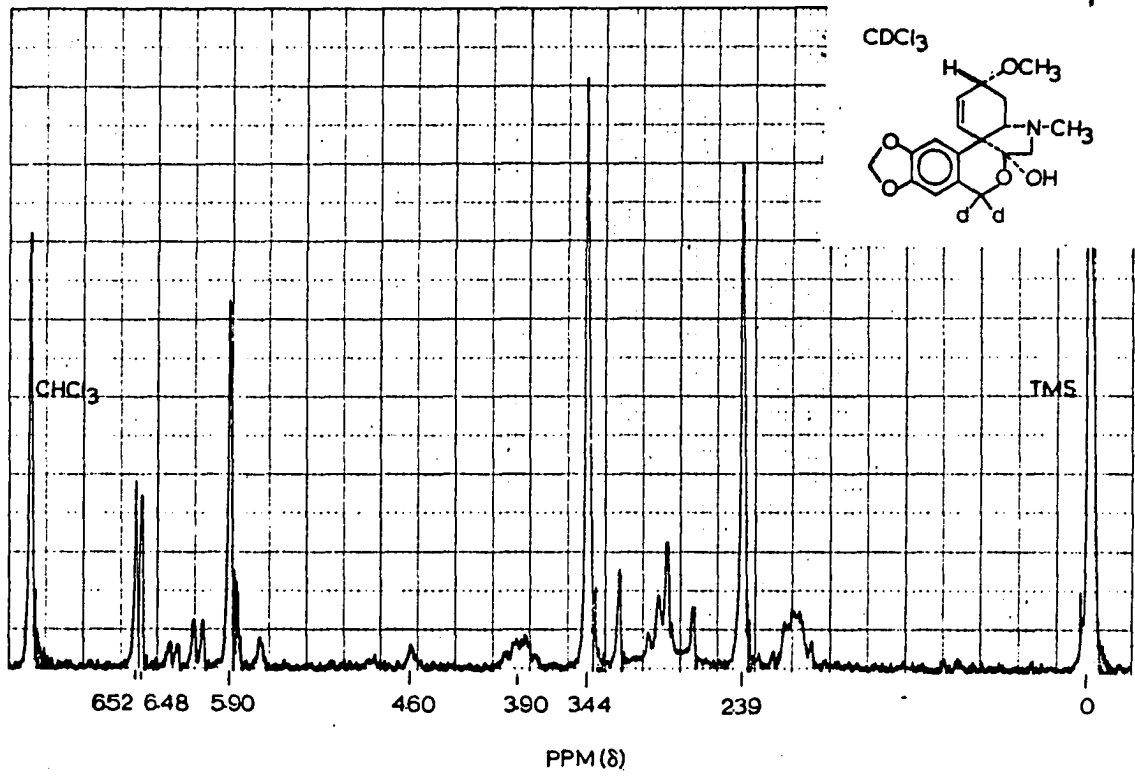
WHERE³⁰ AND FURTHER INTERPRETATION IS NOT PRESENTED HERE. OF IMMEDIATE IMPORTANCE IS THE AB PATTERN ($J_{AB} = 15.0$ C.P.S.) AT 4.8 P.P.M. ASSIGNED TO THE BENZYLIC PROTONS. CLEARLY, IF ONE OR TWO DEUTERIUM ATOMS WERE SUBSTITUTED IN THE BENZYLIC POSITION, THE N.M.R. SPECTRUM COULD BE USED FOR VERIFICATION. THUS IF A DEUTERIUM ATOM WAS INTRODUCED INTO THE C-11 POSITION OF 6-HYDROXYCRINAMINE AND THE 6-HYDROXYCRINAMINE REARRANGED TO CRIWELLINE, ONE OF THE BENZYLIC PROTON PEAKS SHOULD BE ABSENT IN THE N.M.R. SPECTRUM IF THE PROPOSED MECHANISM IS CORRECT.

ACCORDINGLY, 6-HYDROXYCRINAMINE-6,11-D₂ (56) WAS PREPARED AS DESCRIBED EARLIER IN THIS THESIS. THE N.M.R. SPECTRUM OF 56 (FIG. 13B) INDICATED THAT THE DEUTERIUM ATOMS ARE IN THE PRESCRIBED POSITIONS. THE REARRANGEMENT OF 6-HYDROXYCRINAMINE-6,11-D₂ TO CRIWELLINE-8-D₂ WAS CARRIED OUT. THE N.M.R. SPECTRUM OF CRIWELLINE-8-D₂ (94)(FIG. 25A) IS SIMILAR TO THAT



OF CRIWELLINE EXCEPT THE AB PATTERN ASSIGNED TO THE BENZYLIC PROTONS IS ABSENT. IN ITS PLACE ARE TWO SMALL PEAKS ORIGINALLY THOUGHT TO BE IMPURITIES BUT NOW ARE THOUGHT TO BE A SMALL AMOUNT OF MONODEUTERATED CRIWELLINE (A FULL ACCOUNT OF THIS AS-

FIG. 25: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: CRIWELLINE-8-D₂ (94)
B: 6A-DEOXY-8-METHOXYCRIWELLINE (117)



PECT OF THE MECHANISM IS PRESENTED IN THE SECTION ON THE BIOSYNTHESIS OF CRIWELLINE). THE INFRARED SPECTRUM OF CRIWELLINE-8-D₂ SHOWED BANDS (FIG. 6C) ATTRIBUTABLE TO C-D STRETCHING FREQUENCIES AT 4.52 AND 4.75 μ . THESE RESULTS SHOW THAT THE CONVERSION OF 6-HYDROXYCRINAMINE TO CRIWELLINE MAY BE EXPLAINED AT LEAST PARTLY BY A MECHANISM INVOLVING A HYDRIDE SHIFT.

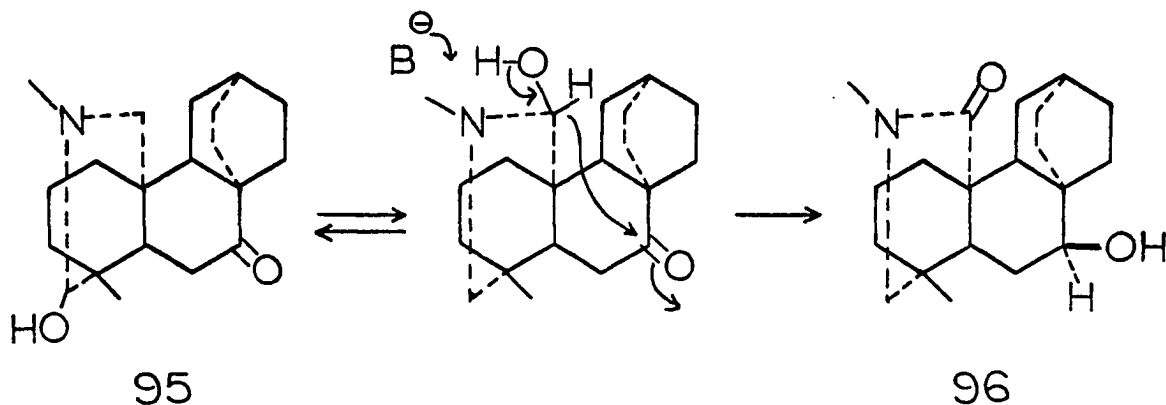
THE HYDRIDE SHIFT FROM THE PYRROLIDINE RING TO THE ALDEHYDE CARBON IS FAVORED STERICALLY BY THE PROPINQUITY OF THE C-11 PROTON TO THE ALDEHYDE CARBON AND THE STEREOCHEMISTRY OF THE C-11 POSITION. THE DRIVING FORCE FOR THE REACTION MUST BE THE GREATER STABILITY OF THE 3-PYRROLIDONE-BENZYL ALCOHOL PAIR VERSUS THE 3-PYRROLIDINOL-BENZALDEHYDE PAIR. THE STABILITY OF CYCLOPENTANONES IS WELL KNOWN⁵⁹ AND MAY BE THE IMPORTANT FACTOR FORCING THE REARRANGEMENT. THE REDUCTION OF AROMATIC ALDEHYDES WITH HYDRIDE ION IS ALSO A WELL KNOWN PROCEDURE IN ORGANIC CHEMISTRY.⁶⁰, P. 630

THE RELATIVE STABILITIES OF THE 3-PYRROLIDONE-BENZYL ALCOHOL PAIR AND THE HEMIKETAL FORM ARE NOT READILY EXPLAINED. THERE HAS NEVER BEEN ANY EVIDENCE SUPPORTING THE OPEN CHAIN FORM OF CRIWELLINE OR TAZETTINE. ALTHOUGH IT IS POSSIBLE THAT SOME OF THE OPEN CHAIN FORM EXISTS IN ACID SOLUTION NO KETONE HAS BEEN TRAPPED IN THIS MEDIA. GENERALLY THE SOLUTIONS ARE MADE BASIC FOR THE ISOLATION OF THE ALKALOID OR DERIVATIVE, A CONDITION WHICH APPARENTLY FAVORS THE CYCLIZED FORM. ALSO NO REACTION HAS BEEN REPORTED SHOWING THE REACTION OF THE POTEN-

TIAL KETONE WITH ANY REAGENT. SINCE THE HEMIKETAL FORM PRE-
 DOMINATES TO SUCH AN EXTENT, THE FACTORS FAVORING ITS STABILI-
 TY SHOULD BE EVIDENT. THE MOST PROBABLE EXPLANATION IS THAT
 THE OPEN CHAIN FORM ENCOUNTERS STERIC INTERACTION WHEREAS THE
 HEMIKETAL IS VIRTUALLY STRAIN FREE. SOME EXPERIMENTAL DATA
 WILL BE PRESENTED IN THE SECTION ON THE N.M.R. SPECTRA OF TAZ-
 ETTINE AND CRIWELLINE DERIVATIVES TO SUPPORT THE CONCEPT OF
 STERIC INTERACTION IN THE OPEN CHAIN FORM.

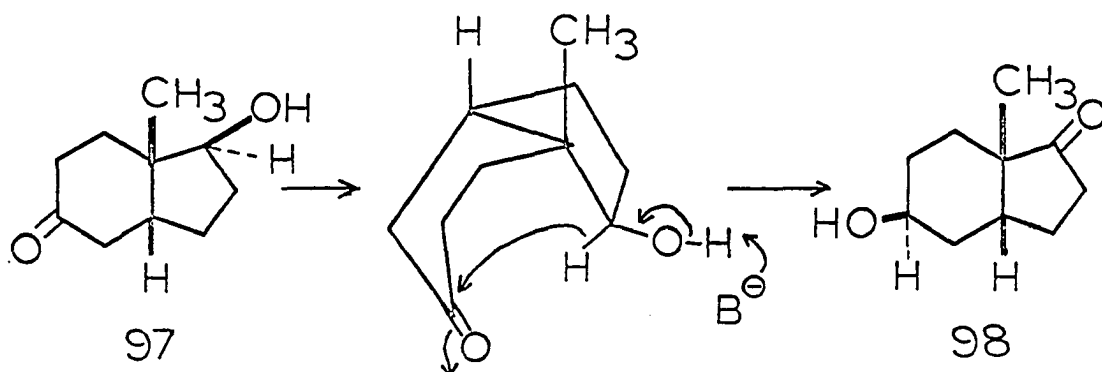
AN INTRAMOLECULAR DISPROPORTIONATION AS SHOWN BY THE
 6-HYDROXYCRINAMINE-CRIWELLINE REARRANGEMENT IS NOT COMMON IN
 ORGANIC CHEMISTRY. THE FACT THAT THE CONVERSION IS STEREO-
 SPECIFIC ADDS TO THE NOVELTY OF THE REACTION.

A SIMILAR DISPROPORTIONATION HAS BEEN NOTED DURING THE
 STRUCTURE PROOF OF AJACONINE.⁶¹ IT WAS FOUND THAT THE CARBIN-
 OL AMINE 95 IN REFLUXING SODIUM METHOXIDE IN METHANOL IS CON-
 VERTED TO A COMPOUND CONTAINING A LACTAM AND A HYDROXYL GROUP.
 FURTHER EXPERIMENTATION SHOWED THE LACTAM TO BE 96. AN IM-
 PORTANT CRITERIA FOR THIS REACTION IS THAT THE B RING MUST BE



IN THE BOAT CONFORMATION IN ORDER TO OBTAIN THE HYDROXYL GROUP TRANS TO THE HETERO BRIDGE.

IN ANOTHER ANALOGOUS REACTION PRELOG AND ACHLIN⁶² FOUND THAT WHEN 1-HYDROXY-8-METHYL-CIS-1-HYDRINDANONE (97) WAS CHROMATOGRAPHED OVER ALUMINA, 5-HYDROXY-8-METHYL-CIS-1-HYDRINDANONE (98) WAS ELUTED. THE REARRANGEMENT ON THE SURFACE OF THE ALUMINA MUST INVOLVE A HYDRIDE TRANSFER. A FACTOR IN FAVOR OF THIS TRANSFER IS THE CIS RING FUSION WHICH ENABLES THE HYDROGEN AT POSITION 1 TO COME INTO CLOSE PROXIMITY OF THE CYCLOHEXANONE CARBONYL. AGAIN THE REACTION IS STEREOSPECIFIC. THERMODYNAMIC CONTROL IS PROBABLY THE DOMINANT FEATURE OF THE REACTION BECAUSE OF THE GREATER STABILITY OF THE CYCLOPENTANONE AS COMPARED TO THE CYCLOHEXANONE.⁵⁹



THE N.M.R. SPECTRA OF SOME TAZETTINE AND CRIWELLINE DERIVATIVES

A NUMBER OF DERIVATIVES OF CRIWELLINE AND TAZETTINE ARE KNOWN WHOSE STRUCTURES HAVE BEEN PROVEN BY CLASSICAL CHEMICAL METHODS, INFRARED AND ULTRAVIOLET SPECTROSCOPY. TO VERIFY THE STRUCTURES OF THESE DERIVATIVES, THEIR N.M.R. SPECTRA HAVE BEEN

OBTAINED AND ANALYZED. IN SO DOING SEVERAL INTERESTING STRUCTURAL EFFECTS WERE NOTED AND IN ONE CASE, AN INCORRECT ASSIGNMENT WAS FOUND. EACH OF THE COMPOUNDS CITED WAS FOUND TO HAVE PHYSICAL PROPERTIES IN SATISFACTORY AGREEMENT WITH THE RESPECTIVE LITERATURE VALUES.

IKEDA ET AL.¹⁰ REPORTED THAT UPON HEATING TAZETTINE IN STRONG ACID, TAZETTINOL (11) AND ISOTAZETTINOL (12) ARE OBTAINED. HOWEVER, THIS AUTHOR WAS SUCCESSFUL IN ISOLATING ONLY ISOTAZETTINOL. THE LOW FIELD SINGLETS IN THE N.M.R. SPECTRUM OF ISOTAZETTINOL (FIG. 26A) AT 6.46 AND 6.56 P.P.M. ARE ASSIGNED TO THE AROMATIC PROTONS. THE OLEFINIC PROTONS GIVE RISE TO THE AB PART ($J_{AB} = 10.5$ C.P.S.) OF AN ABX PATTERN. THE METHYLENEDIOXY PROTONS PRODUCE A SINGLET AT 5.90 P.P.M. AND THE BENZYLIC PROTONS FORM AN AB PATTERN ($J_{AB} = 15.1$ C.P.S.) AT 4.95 AND 4.65 P.P.M. THE C-3 PROTON MULTIPLET APPEARS AT 4.10 P.P.M. THE ONE PROTON MULTIPLET AT 3.00 P.P.M. IS PRODUCED BY THE 4A PROTON AND THE TWO PROTON MULTIPLET AT 1.90 P.P.M. IS ASSIGNED TO THE C-4 PROTONS. THE AB PATTERN ($J_{AB} = 10.8$ C.P.S.) AT 2.63 AND 3.40 P.P.M. IS ASSIGNED TO THE C-6 PROTONS.

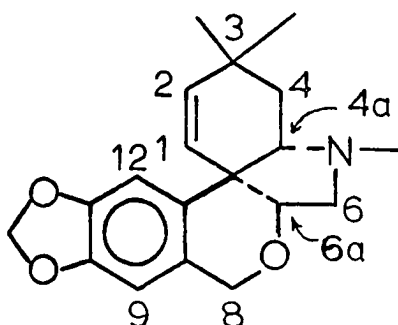
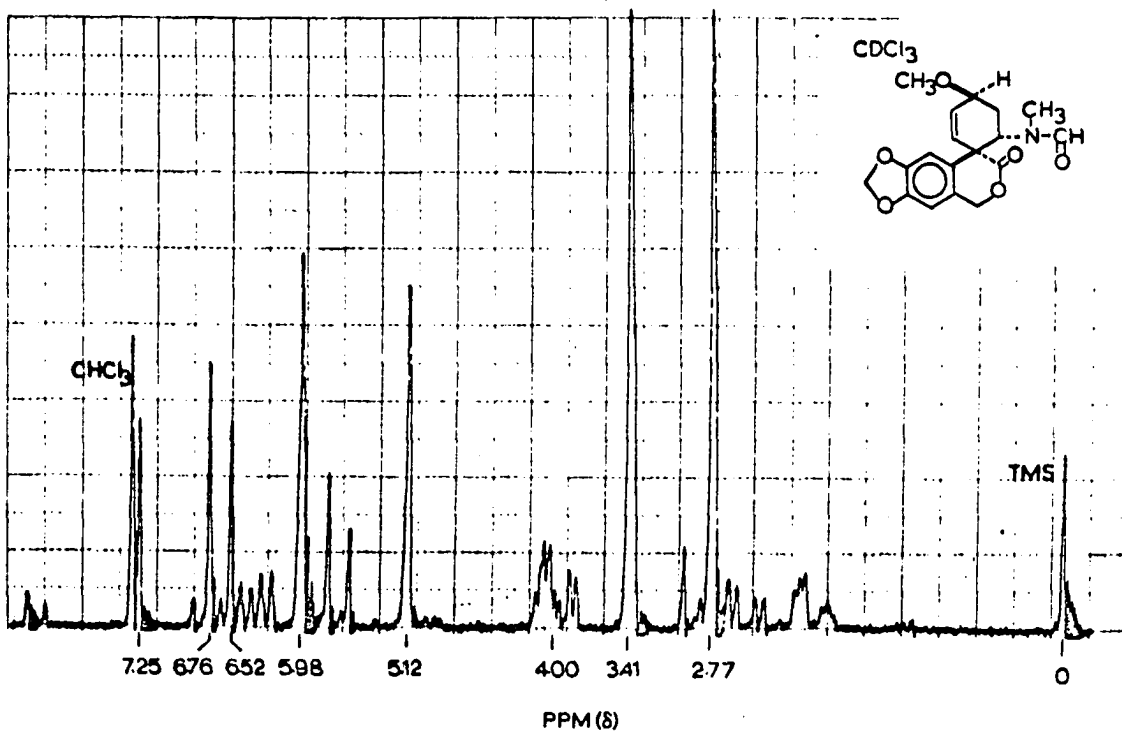
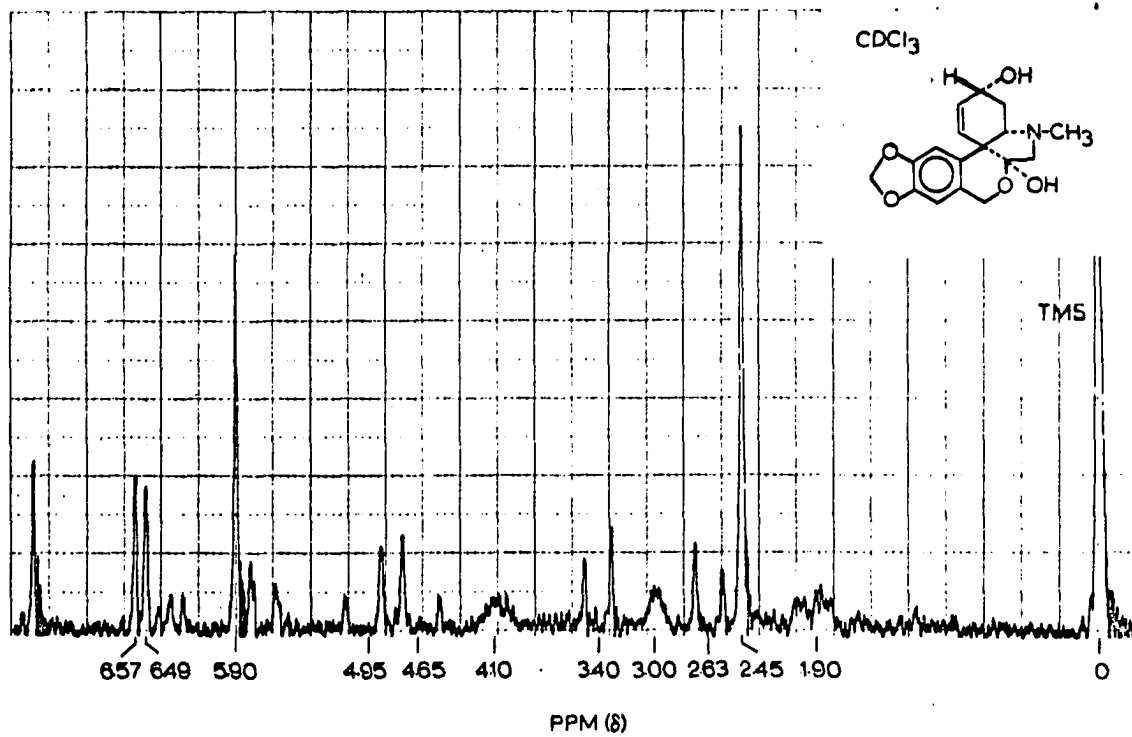


FIG. 26: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: ISOTAZETTINOL (12)
B: TAZETTAMIDE (14)



THE N-METHYL PROTONS GIVE THE EXPECTED SINGLET AT 2.45 P.P.M. THE INTEGRAL OF THE SPECTRUM OF THE SAMPLE WITH A FEW DROPS OF DEUTERIUM OXIDE ADDED SHOWED THAT TWO BROAD ONE PROTON PEAKS WERE REMOVED FROM THE 2-3 P.P.M. REGION. THE N.M.R. SPECTRUM OF 12 IS IN ACCORD WITH ITS PROPOSED STRUCTURE.

MANGANESE DIOXIDE OXIDIZES CRIWELLINE AND TAZETTINE TO CRIWELLAMIDE (38) AND TAZETTAMIDE (14), RESPECTIVELY. THE N.M.R. SPECTRUM OF TAZETTAMIDE IS SHOWN IN FIG. 26B. THE SINGLET AT 7.32 P.P.M. IS RESIDUAL CHLOROFORM IN THE DEUTERIOCHLOROFORM SOLVENT. THE SINGLET AT 7.25 P.P.M. MUST BE ASSIGNED TO THE FORMAMIDE PROTON. THE AROMATIC PROTONS GIVE THE EXPECTED SINGLETS AT 6.76 AND 6.52 P.P.M. AND THE OLEFINIC PROTONS FORM THE AB PART ($J_{AB} = 10.6$ C.P.S.) OF AN ABX PATTERN. THE SINGLETS AT 5.98 AND 5.12 P.P.M. ARE ASSIGNED TO THE METHYLENEDIOXY AND BENZYLIC PROTONS, RESPECTIVELY. THE MULTIPLETS AT 4.00 P.P.M. ARE APPARENTLY PRODUCED BY THE PROTONS AT C-3 AND C-4A. THE METHOXYL AND N-METHYL PROTONS GIVE RISE TO SINGLETS AT 3.41 AND 2.77 P.P.M., RESPECTIVELY. THE N.M.R. SPECTRUM OF CRIWELLAMIDE IS VERY SIMILAR TO THAT OF TAZETTAMIDE AND IS NOT PRESENTED.

THE N.M.R. SPECTRA OF DIHYDROCRIWELLINE (99) AND DIHYDROTAZETTINE (100) WERE OBTAINED TO TEST A POSTULATE PUT FORTH BY HAUGWITZ, JEFFS AND WENKERT.³⁰ THESE AUTHORS PROPOSED THAT THE CONFORMATION OF RING B OF CRIWELLINE MUST BE SUCH THAT THE C-12 PROTON IS LOCATED OVER THE SHIELDING AREA OF THE DOUBLE BOND IN RING C. THE BASIS FOR THIS PROPOSAL IS THAT THE C-12

PROTON OF CRIWELLINE PRODUCES A PEAK IN THE N.M.R. SPECTRUM OF CRIWELLINE THAT IS 0.27 P.P.M. UPFIELD FROM THE C-12 PROTON PEAK OF TAZETTINE. THIS OBSERVATION WAS INTERPRETED TO MEAN THAT THE C-12 PROTON OF CRIWELLINE MUST BE IN THE SHIELDING AREA OF THE DOUBLE BOND, A CIRCUMSTANCE DEPENDENT UPON THE CONFORMATION OF THE B RING. THIS POSTULATION WAS PRESENTED WITHOUT THE BENEFIT OF COMPARISON WITH THE CHEMICAL SHIFTS OF THE C-12 PROTONS OF THE CORRESPONDING DIHYDRO DERIVATIVES.

IT SEEMED REASONABLE TO TEST THIS POSTULATE, NOT ONLY FOR ITS VALIDITY BUT ALSO FOR ITS POTENTIAL USE IN STRUCTURE ELUCIDATIONS. IF THE PROPOSAL IS CORRECT THEN THE C-12 PROTON PEAK OF CRIWELLINE WILL SHIFT FURTHER DOWNFIELD THAN THE CORRESPONDING PROTON PEAK OF TAZETTINE, UPON HYDROGENATION. THE N.M.R. SPECTRA OF DIHYDROCRIWELLINE AND DIHYDROTAZETTINE ARE SHOWN IN FIGS. 27A AND 27B, RESPECTIVELY. THE METHYLENEDIOXY PROTONS OF DIHYDROCRIWELLINE GIVE A SINGLET AT 5.91 P.P.M. AND THE BENZYLIC PROTONS ARE ASSIGNED TO THE AB PATTERN ($J_{AB} = 14.2$ C.P.S.) AT 4.75 AND 4.47 P.P.M. THE METHOXYL AND N-METHYL SINGLETS APPEAR AT 3.39 AND 2.25 P.P.M., RESPECTIVELY. SIMILAR ASSIGNMENTS APPLY TO THE N.M.R. SPECTRUM OF DIHYDROTAZETTINE. THE AROMATIC PROTONS ARE ASSIGNED ON THE BASIS OF THE COUPLING TO THE BENZYLIC PROTONS (THE SHORTER PEAK CORRESPONDS TO THE C-9 PROTON). THE RESPECTIVE CHEMICAL SHIFTS ARE LISTED IN TABLE 2 FOR THE ALKALOIDS AND THEIR DIHYDRO DERIVATIVES.

THE TABULATED DATA SHOWS THAT HYDROGENATION HAS THE GREAT-

FIG. 27: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: DIHYDROCRIVELLINE (99)

B: DIHYDROTAZETTINE (100)

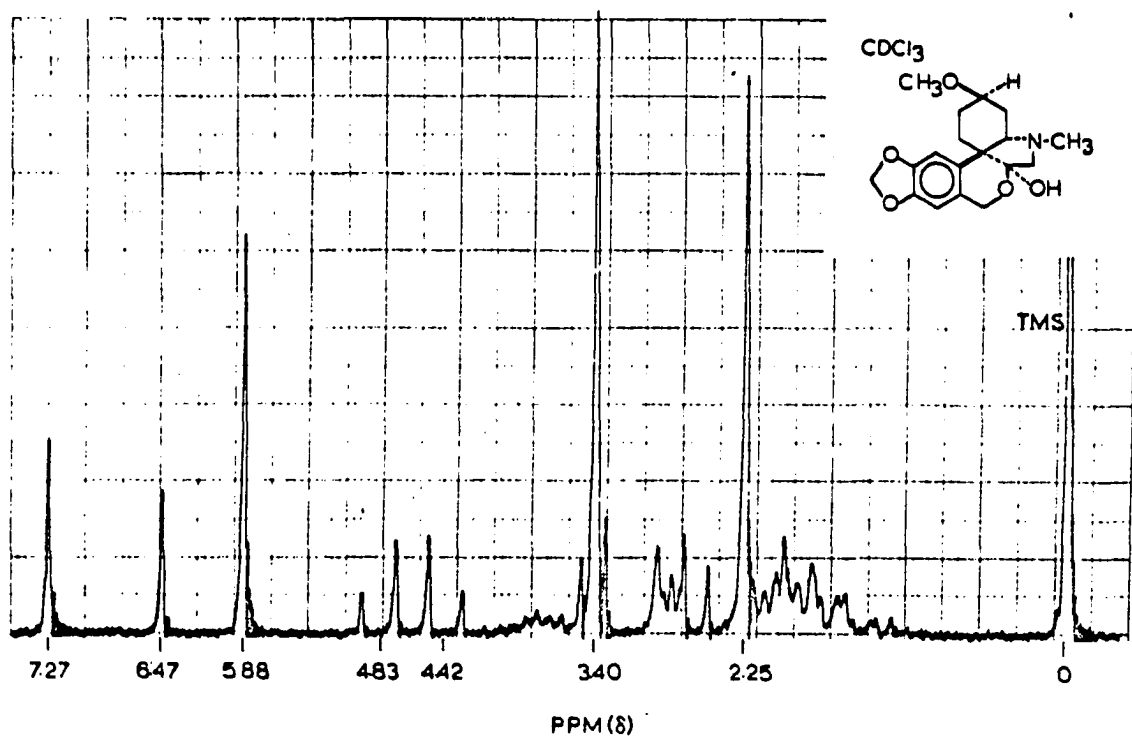
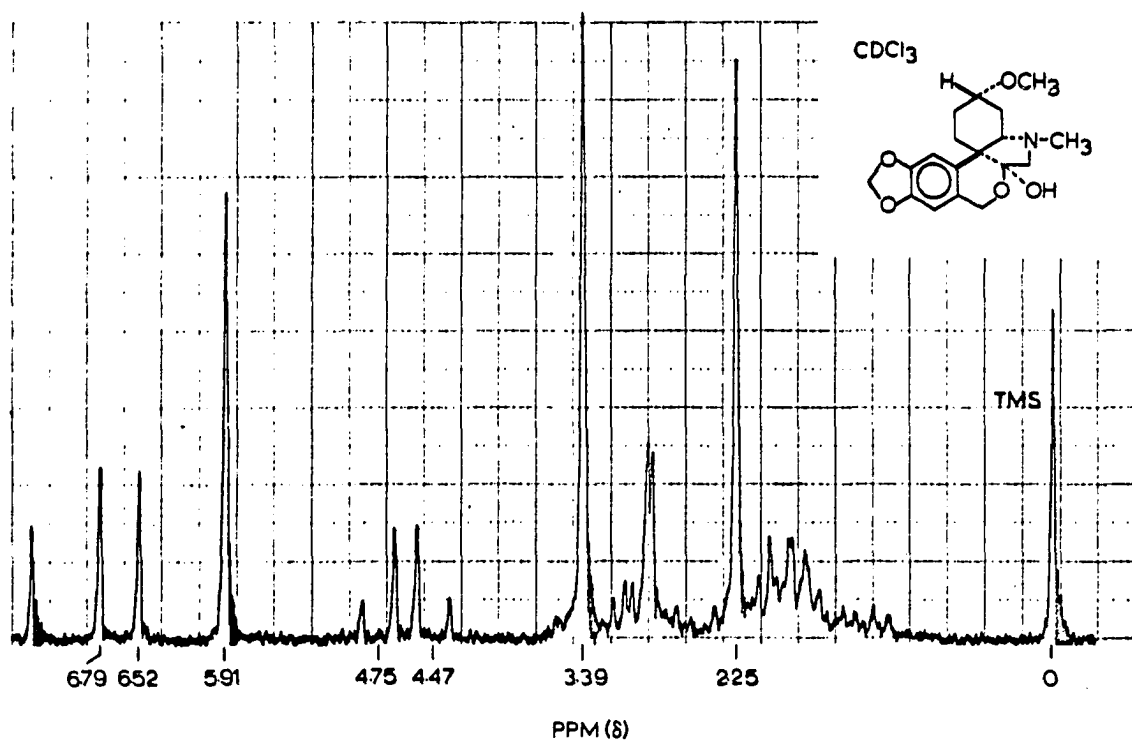


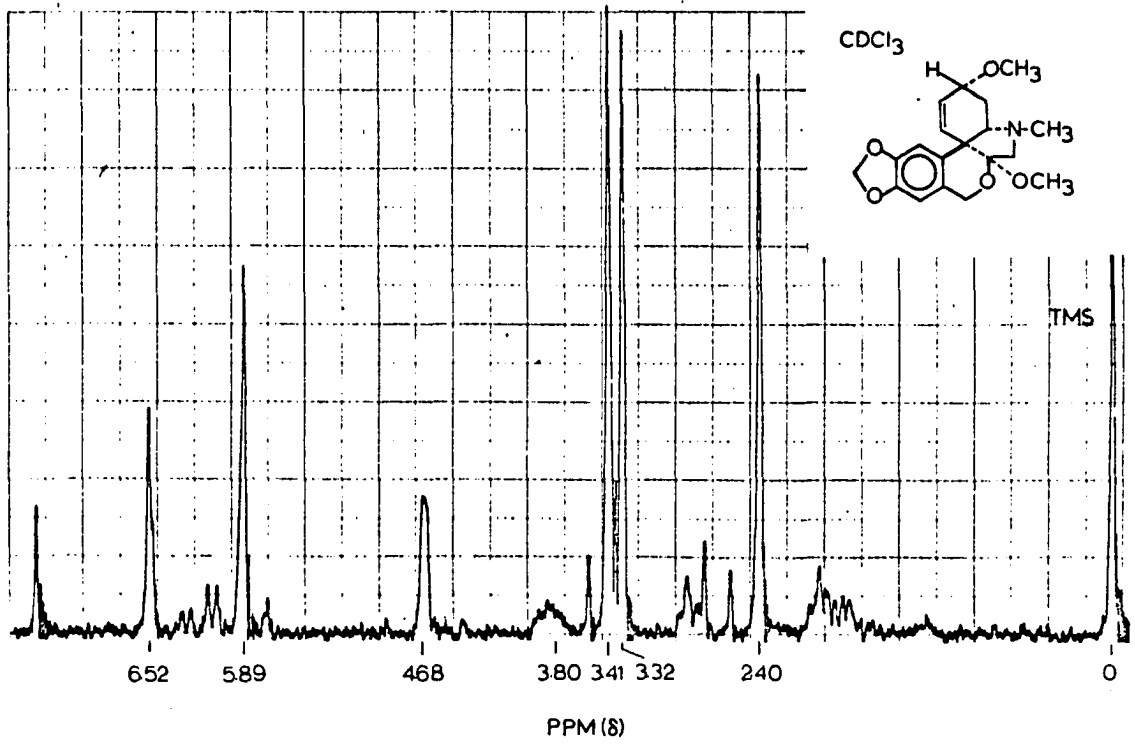
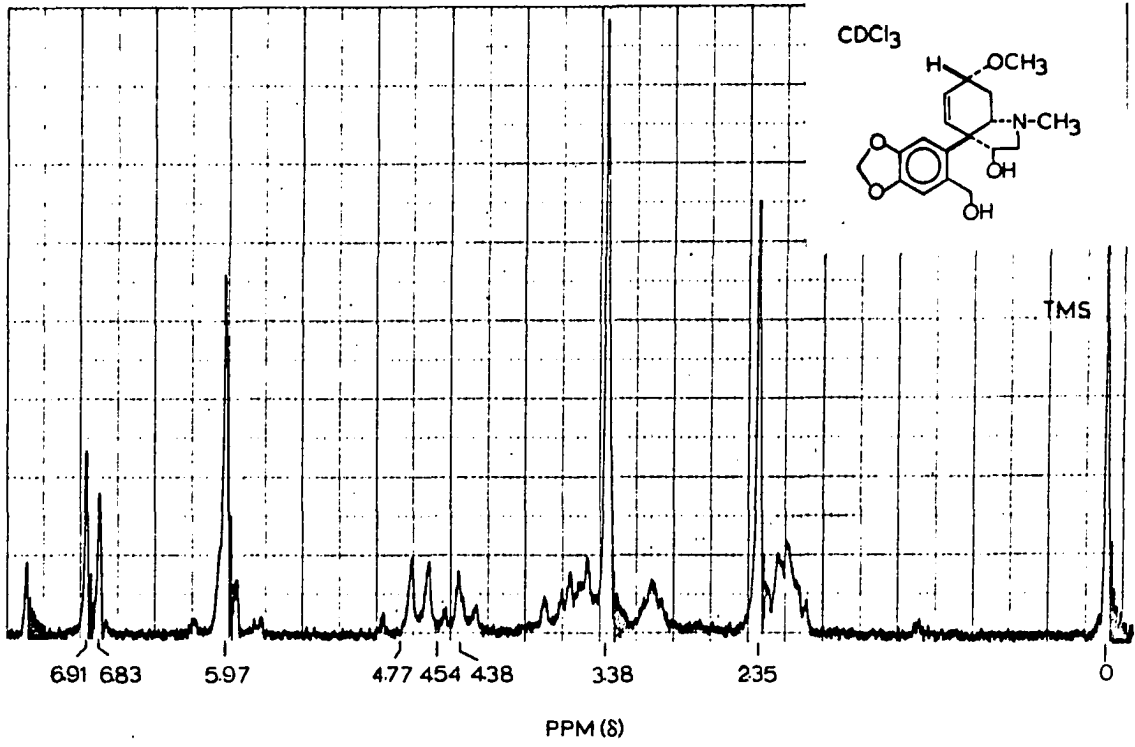
TABLE 2. CHEMICAL SHIFTS (δ) OF THE AROMATIC PROTONS OF CRIWELLINE, TAZETTINE AND THEIR DIHYDRO DERIVATIVES

COMPOUND	C-9 PROTON	C-12 PROTON	DIFFERENCE
CRIWELLINE	6.48	6.52	
DIHYDROCRIWELLINE	6.52	6.79	0.27
TAZETTINE	6.50	6.79	
DIHYDROTAZETTINE	6.47	7.27	0.48

EST EFFECT UPON THE CHEMICAL SHIFT OF THE C-12 PROTON OF TAZETTINE, IN DIRECT CONTRAST WITH THE POSTULATE. THUS THE C-12 PROTON OF TAZETTINE MUST BE CLOSER TO THE DOUBLE BOND THAN THE CORRESPONDING RELATIONSHIP IN CRIWELLINE. THE LARGE DIFFERENCE IN CHEMICAL SHIFTS OF THE C-12 PROTONS OF THE DIHYDRO DERIVATIVES SUGGESTS THAT THERE MUST BE SOME ANISOTROPY EFFECT IN TAZETTINE WHICH ACTS MORE STRONGLY THAN IN CRIWELLINE. THE ONLY LIKELY GROUP THAT COULD PRODUCE SUCH AN EFFECT IS THE METHOXYL GROUP, HOWEVER MODELS SHOW THAT THE METHOXYL GROUP IS A CONSIDERABLE DISTANCE FROM THE C-12 PROTON. NO FURTHER EXPLANATION IS AVAILABLE AT THIS TIME.

PREVIOUSLY IT WAS STATED THAT CONSIDERABLE STERIC INTERACTION OCCURRED IN THE 5,10B-ETHANOPHENANTHRIDINE ALKALOIDS IF NO BOND IS PRESENT BETWEEN THE NITROGEN AND C-6. AN ILLUSTRATION OF THIS EFFECT IS FOUND IN THE N.M.R. SPECTRA OF CRIWELLINEDIOL (101) AND TAZETTADIOL (5). THE N.M.R. SPECTRUM OF CRIWELLINEDIOL IN DEUTERIOCHLOROFORM (FIG. 2 A) SHOWS PEAKS FOR THE AROMATIC PROTONS AT 6.91 AND 6.83 P.P.M. THE OLEFINIC

FIG. 28: NUCLEAR MAGNETIC RESONANCE SPECTRA
A: CRIWELLINEDIOL (101)
B: O-METHYLCRIWELLINE



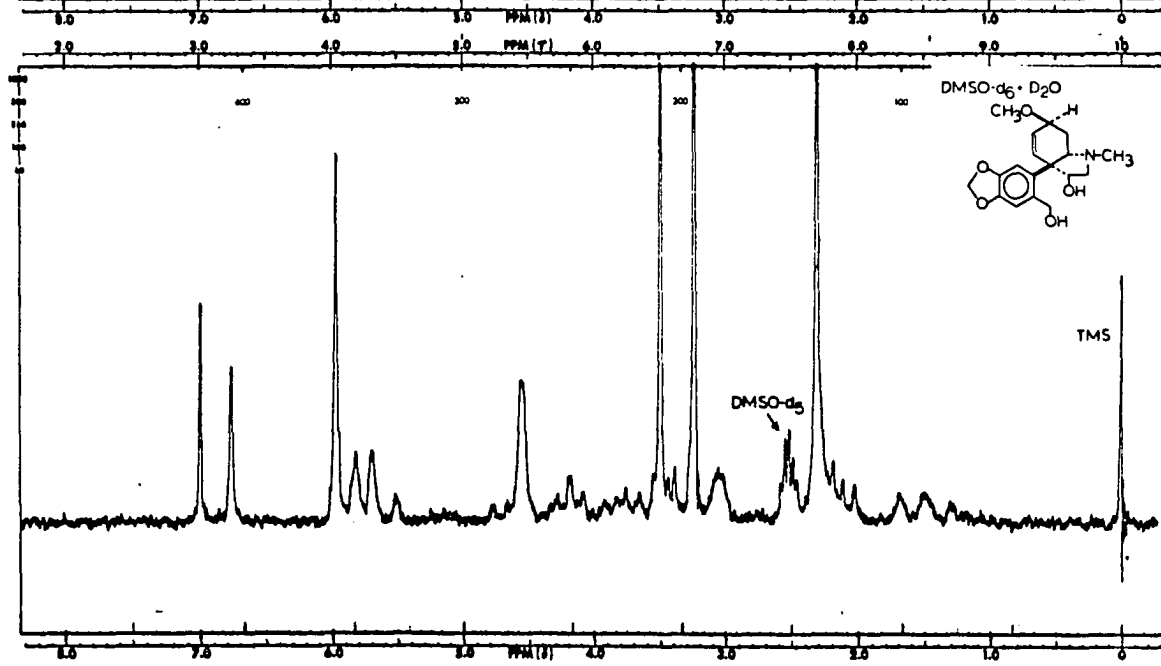
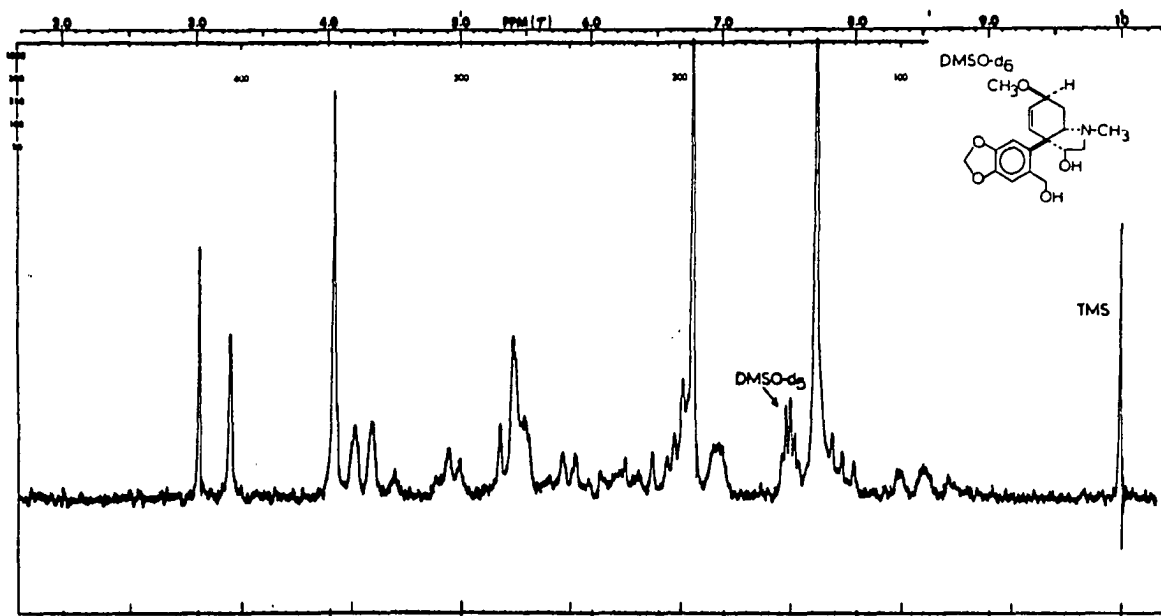
AND METHYLENEDIOXY PROTONS PRODUCE PEAKS CENTERED AT 5.97 P.P.M. THE BENZYLIC PROTONS GIVE RISE TO AN AB PATTERN ($J_{AB} = 11.8$ C.P.S.) CENTERED AT 4.54 AND 4.77 P.P.M. THE C-6A PROTON IS ASSIGNED TO THE TRIPLET AT 4.38 P.P.M. AND THE METHOXYL AND N-METHYL SINGLET APPEAR AT 3.38 AND 2.35 P.P.M., RESPECTIVELY. THE HYDROXYL PROTON PEAKS WERE LOCATED IN THE 2-4 P.P.M. REGION BY DEUTERATION. THE ASSIGNMENT OF INTEREST IS THE AB PATTERN PRODUCED BY THE BENZYLIC PROTONS. NORMALLY METHYLENE PROTONS ARE NOT COUPLED TO EACH OTHER EXCEPT WHEN THE CARBON TO WHICH THEY ARE BONDED IS ATTACHED TO AN ASYMMETRIC CARBON OR IS PART OF A RING.⁴¹, p. 102 SINCE NEITHER OF THESE CRITERIA APPLY IN THIS CASE, ANOTHER EXPLANATION MUST BE ADVANCED. MODELS OF CRIWELLINEDIOL AND TAZETTADIOL REVEAL A CONSIDERABLE AMOUNT OF STERIC INTERACTION EXISTS BETWEEN THE BENZYL ALCOHOL GROUPING AND THE HEXAHYDROINDOLE PORTIONS OF THE MOLECULES. THUS THE BENZYLIC ALCOHOL GROUPING MUST ARRANGE ITSELF IN SUCH A MANNER AS TO HAVE THE LEAST AMOUNT OF STERIC INTERACTION. THE RESULTING CONFORMATION PRODUCES AN ASYMMETRIC ENVIRONMENT FOR THE BENZYLIC PROTONS AND COUPLING IS FOUND IN THE N.M.R. SPECTRA.

IT COULD BE ARGUED THAT A STRONG HYDROGEN BOND MIGHT PRODUCE AN ASYMMETRIC ENVIRONMENT FOR THE BENZYLIC PROTONS, HOWEVER, THE N.M.R. SPECTRUM OF TAZETTADIOL IN DIMETHYLSULFOXIDE- D_6 (FIG. 29A) DISCOUNTS THIS EXPLANATION. THE STRONG HYDROGEN BOND BETWEEN HYDROXYL PROTONS AND DIMETHYLSULFOXIDE WOULD CANCEL ANY INTRAMOLECULAR HYDROGEN BOND. THE C-12 PRO-

FIG. 29: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: TAZETTADIOL (5)

B: 5 + DEUTERIUM OXIDE



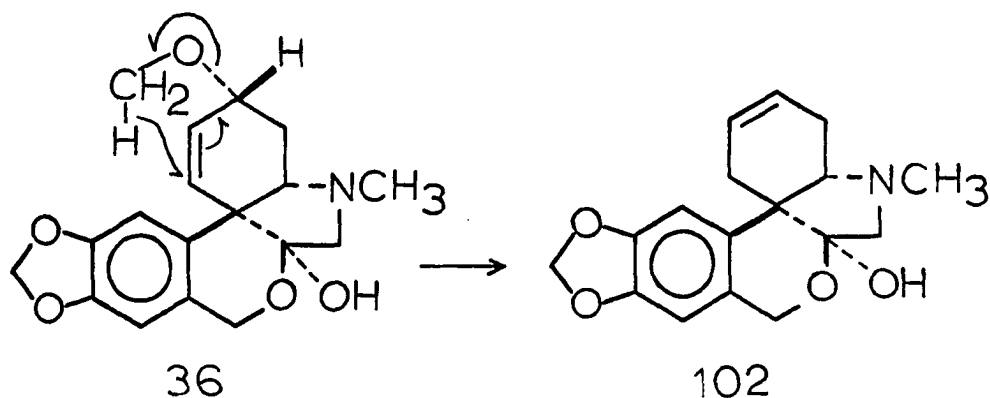
TON OF TAZETTADIOL PRODUCES THE SINGLET AT 7.00 P.P.M. AND THE C-9 PROTON GIVES RISE TO THE PEAK AT 6.77 P.P.M. THE METHYLENEDIOXY PROTONS GIVE A SINGLET AT 5.97 P.P.M. AND THE OLEFINIC PROTONS PRODUCE AN AB PATTERN ($J_{AB} = 10.0$ C.P.S.) AT 5.6 AND 5.9 P.P.M. THE TRIPLET AT 5.1 P.P.M. IS REMOVED UPON DEUTERATION (FIG. 29B) AND MUST BE ASSIGNED TO THE BENZYLIC HYDROXYL PROTON.⁴⁴ THE MULTIPLY AT 4.6 P.P.M. IS ASSIGNED TO THE BENZYLIC PROTONS AND THE C-6A HYDROXYL PROTON. UPON DEUTERATION THIS MULTIPLY COLLAPSES TO AN AB PATTERN ($J_{AB} = 12$ C.P.S.) PRODUCED BY THE BENZYLIC PROTONS. THE QUARTET AT 4.2 P.P.M. BECOMES A TRIPLET UPON DEUTERATION WHICH ESTABLISHES IT AS THE C-6A PROTON RESONANCE. THE CHANGE IN MULTIPLICITY OCCURS BECAUSE OF THE COUPLING TO THE HYDROXYL PROTON WHICH IS REMOVED UPON DEUTERATION. THE C-6A PROTON IS USUALLY A TRIPLET BECAUSE OF THE COUPLING TO THE C-6 PROTONS. THE SINGLETS AT 3.22 AND 2.30 P.P.M. ARE PRODUCED BY THE METHOXYL AND N-METHYL PROTONS, RESPECTIVELY.

A COMPARISON OF THE SPECTRA OF THE EPIMERIC COMPOUNDS AND THE INFORMATION DERIVED THEREFROM ILLUSTRATES THE VALUE OF USING DIFFERENT SOLVENTS IN N.M.R. STUDIES.

MASS SPECTRA OF CRIWELLINE AND TAZETTINE

AS WITH 6-HYDROXYCRINAMINE AND HAEMANTHIDINE, THE EPIMERIC C-3 POSITION OF CRIWELLINE AND TAZETTINE PLAYS AN IMPORTANT ROLE IN THEIR RESPECTIVE FRAGMENTATIONS IN THE MASS SPECTROMETER. THUS CRIWELLINE AND TAZETTINE GIVE RISE TO THE MASS SPECTRA SHOWN IN FIGS. 30A AND 31A, RESPECTIVELY.

THE MASS SPECTRUM OF CRIWELLINE CONTAINS A PROMINENT PEAK AT M/E 301 AS WELL AS A PEAK FOR THE MOLECULE ION AT M/E 331. THE MASS SPECTRUM OF CRIWELLINE-N-D₃ (FIG. 30B) SHOWS A SHIFT IN THESE PEAKS TO M/E 304 AND M/E 334. THE LOSS OF 30 MASS UNITS FROM THE PARENT ION TO GIVE 102 MAY BE EXPLAINED BY THE LOSS OF FORMALDEHYDE. ALSO, A METASTABLE ION PEAK WAS FOUND IN THE MASS SPECTRUM OF CRIWELLINE AT M/E 274 IN GOOD AGREEMENT WITH THE THEORETICAL VALUE ($301^2/331 = 273.7$).

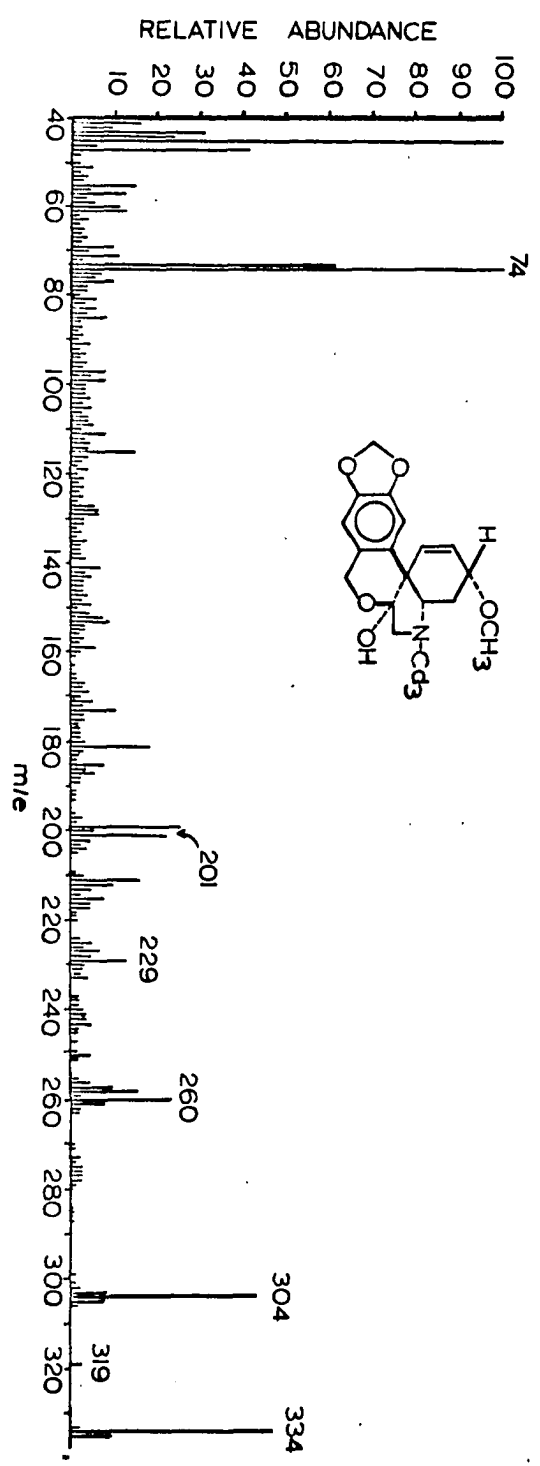
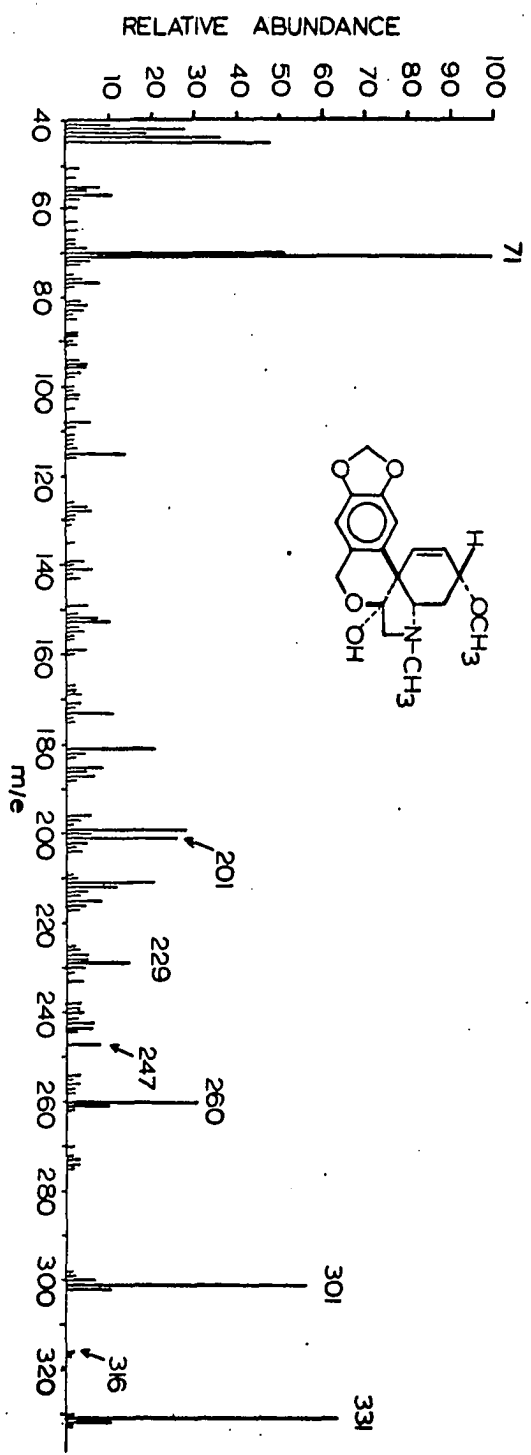


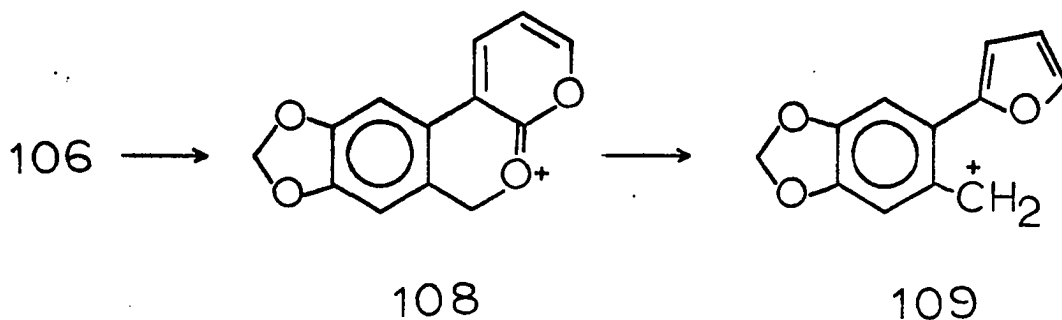
THE PEAKS AT M/E 316 AND M/E 298 IN THE MASS SPECTRA OF CRIWELLINE AND TAZETTINE SUGGEST SUCCESSIVE LOSSES OF A METHYL RADICAL AND WATER. A POSSIBLE SCHEME FOR THE FORMATION OF THESE IONS IS $36 \rightarrow 103 \rightarrow 104$ AND IS SUPPORTED BY METASTABLE IONS AT MASSES 302 ($316^2/331 = 301.7$) AND AT 281.0 ($298^2/316 = 281.0$). THE INTENSE PEAK AT M/E 260 IN THE SPECTRUM OF CRIWELLINE REMAINS AT THE SAME MASS UNIT IN THE SPECTRUM OF CRIWELLINE-N-D₃. THIS ION PROBABLY ARISES BY A RETRO DIELS-ALDER REACTION TO GIVE 105 WHICH FRAGMENTS TO 106 (M/E 260) AND 107 (M/E 71). THE LATTER FRAGMENT ACCOUNTS FOR THE BASE PEAK IN THE SPECTRUM AND IS SUPPORTED BY A SHIFT TO M/E 74 IN THE MASS

FIG. 30: MASS SPECTRA

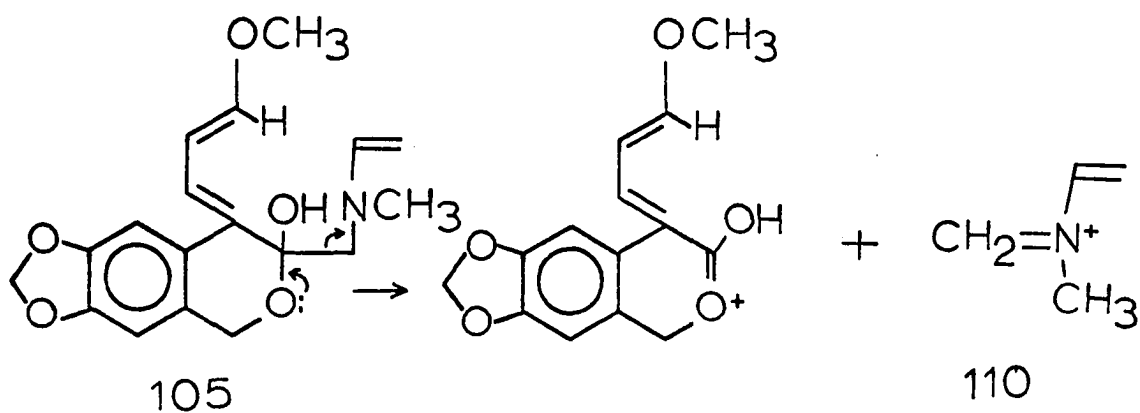
A: CRIWELLINE (36)

B: CRIWELLINE-N-D₃





THE ABUNDANT ION AT m/e 70 IN THE MASS SPECTRA OF CRIWEL-LINE AND TAZETTINE MAY ARISE FROM THE FRAGMENTATION OF 105. CLEAVAGE α TO THE NITROGEN WOULD GIVE THE ION 110 (m/e 70). THIS ION DOES NOT ARISE FROM THE LOSS OF A PROTON FROM THE METHYL GROUP OF 107 BECAUSE A QUANTITATIVE SHIFT TO m/e 73 IS FOUND IN THE SPECTRUM OF THE $-N-D_3$ ANALOGS.

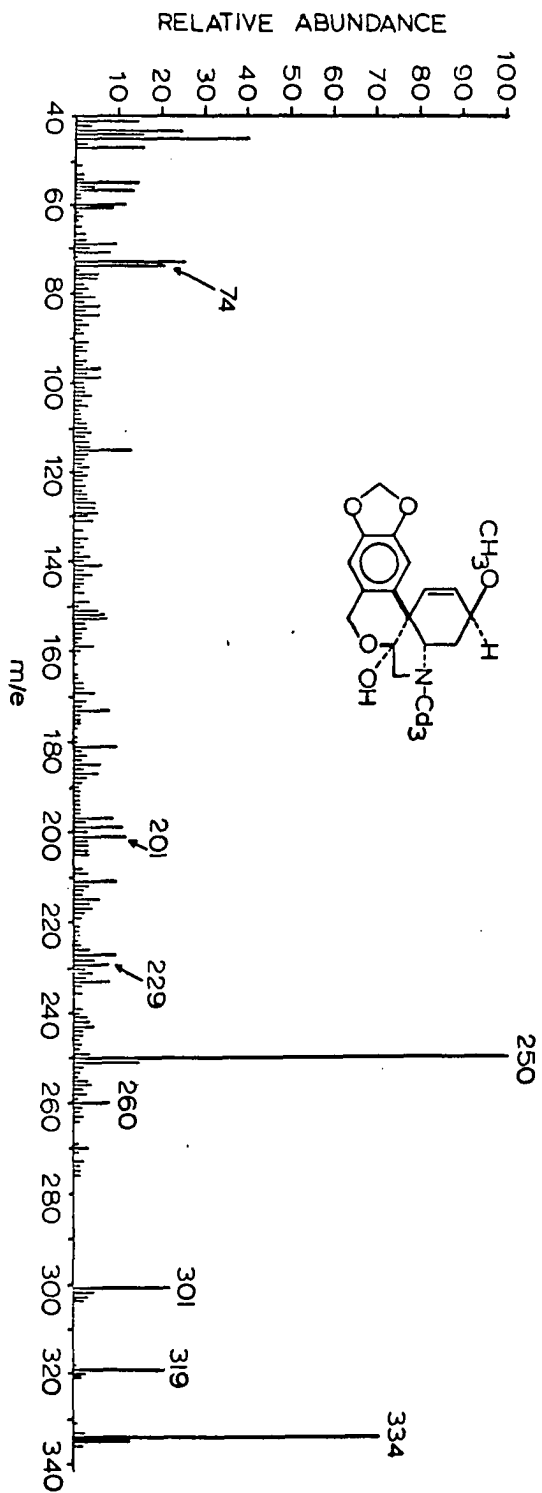
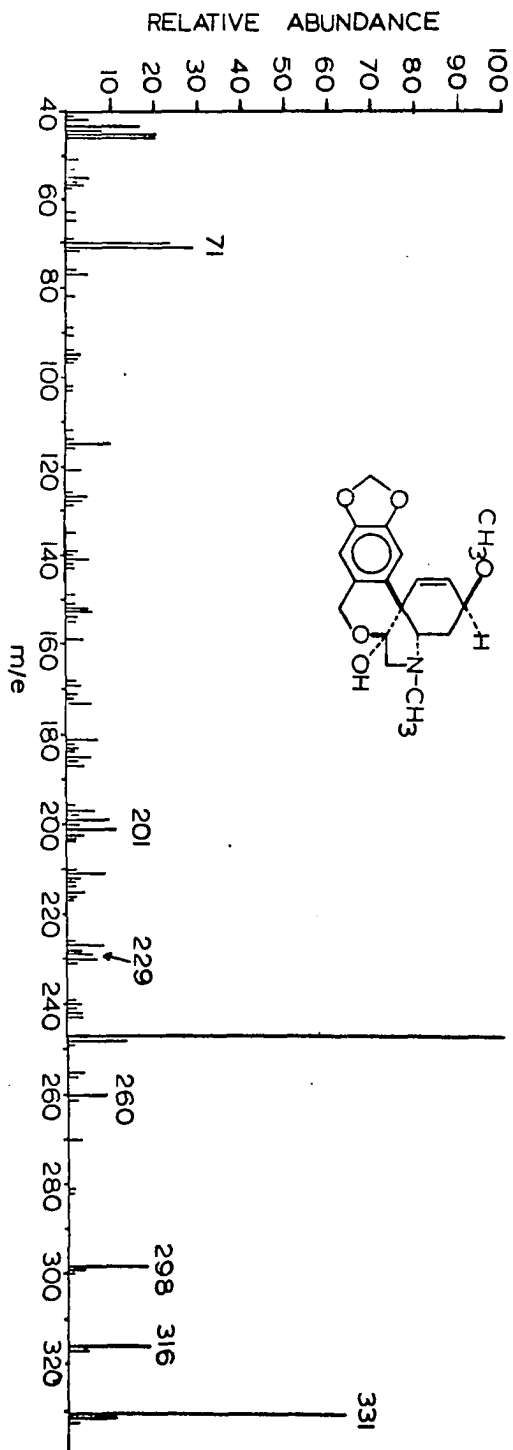


THE MASS SPECTRA OF TAZETTINE AND TAZETTINE- $N-D_3$ (FIGS. 31A AND 31B) SHOW PEAKS AT THE SAME MASSES AS THEIR C-3 EPIMERS BUT AT GREATLY DIFFERENT INTENSITIES. THESE PEAKS ARE ASCRIBED TO IONS OF SIMILAR STRUCTURE AS IN THE FRAGMENTATION OF THE

FIG. 31: MASS SPECTRA

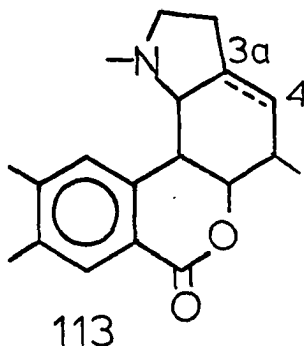
A: TAZETTINE (20)

B: TAZETTINE-N-D₃



CONJUGATION WITH A BENZENE RING CONTAINING A METHYLENEDIOXY SUBSTITUENT. THE N.M.R. SPECTRUM INDICATED THE PRESENCE OF ONE OLEFINIC PROTON IN THE MOLECULE.⁷

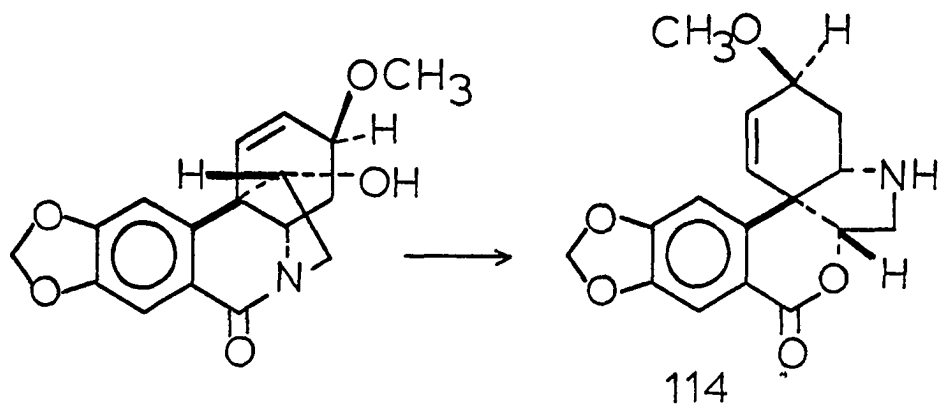
SEVERAL LACTONIC ALKALOIDS HAVE BEEN ISOLATED FROM THE AMARYLLIDACEAE PLANT FAMILY, AND ALL ARE DERIVED FROM THE [2]-BENZOPYRANO[3,4g]INDOLE NUCLEUS (113).¹, P. 329 WHEN THESE ALKALOIDS CONTAIN OLEFINIC UNSATURATION, IT OCCURS AT THE 3A-4 POSITIONS. ALL AVAILABLE CHEMICAL AND SPECTROSCOPIC EVIDENCE INDICATED THAT MACRONINE PROBABLY CONTAINED THIS RING SYSTEM.



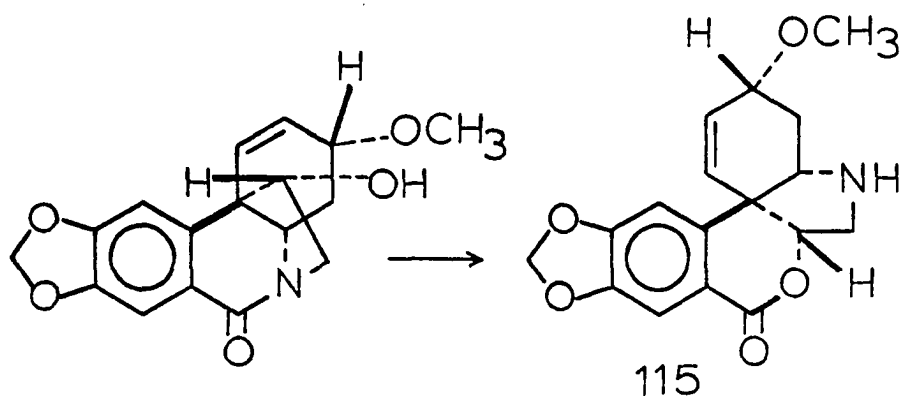
HOWEVER, NO OTHER ALKALOIDS CONTAINING THIS RING SYSTEM WERE ISOLATED FROM C. MACRANTHERUM BUT CRIWELLINE AND CRINAMINE WERE.⁷ THIS OBSERVATION LED THIS AUTHOR TO INVESTIGATE A POSSIBLE RELATIONSHIP BETWEEN MACRONINE AND CRIWELLINE.

THE STRUCTURE OF MACRONINE

IN SOME UNPUBLISHED WORK, WILDMAN (W. C. WILDMAN, PRIVATE COMMUNICATION) HAD NOTED THAT 6-OXOHAEMANTHAMINE WAS CONVERTED TO A LACTONE UPON REFLUXING WITH HYDROXYLAMINE HYDROCHLORIDE WITH SODIUM ACETATE IN ETHANOL. THE STRUCTURE 114 WAS PROPOSED



FOR THIS LACTONE. IT SEEMED REASONABLE THAT 6-OXOCRINAMINE SHOULD UNDERGO A SIMILAR REARRANGEMENT, AND THAT THE REAGENTS USED BY WILDMAN WERE NOT AS IMPORTANT AS THE BUFFERED SOLUTION PRODUCED BY THEM. INDEED 6-OXOCRINAMINE IN AN ACETATE BUFFERED SOLUTION WAS TRANSFORMED INTO THE LACTONE 115. APPARENTLY THE EQUILIBRIUM FAVORS THE STRAIN FREE LACTONE OVER THE STRAINED LACTAM. THE AMINO KETONE 115 ABSORBED IN THE ULTRAVIOLET AT



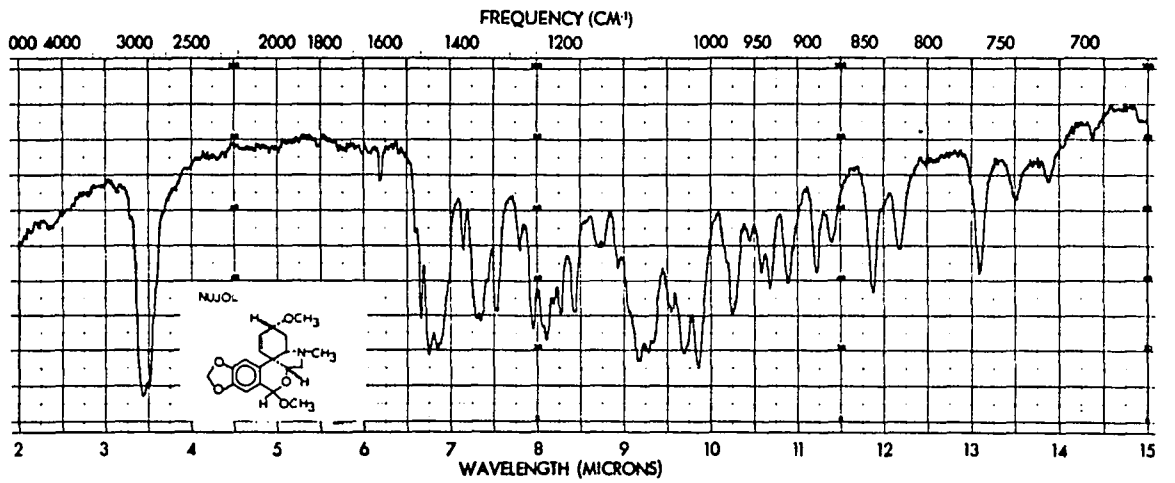
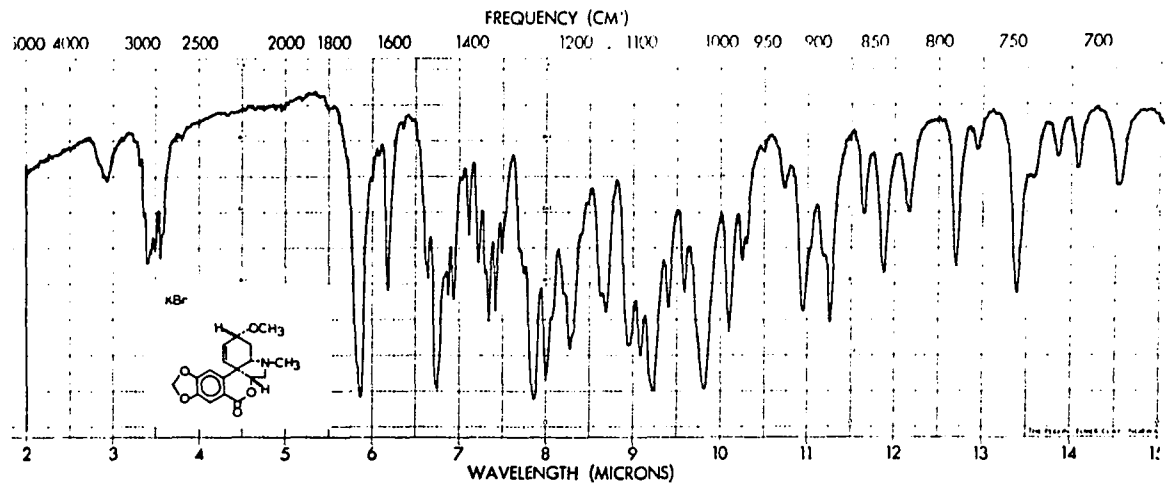
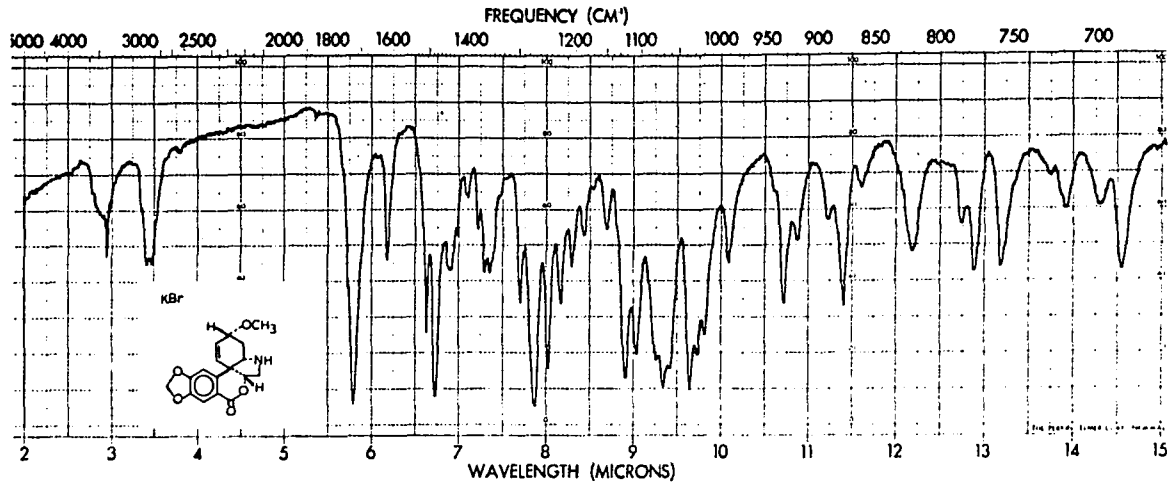
228, 268 AND 305 $m\mu$ AND IN THE INFRARED AT 2.95, 5.79 AND 6.18 μ (FIG. 32A). THE N.M.R. SPECTRUM OF 115 (FIG. 33A) EXHIBITED AROMATIC PROTON RESONANCES AT 6.57 AND 7.49 P.P.M. THE OLEFINIC PROTONS FORM THE AB PART ($J_{AB} = 11.1$ C.P.S.) OF AN

FIG. 32: INFRARED SPECTRA

A: N-DEMETHYLMACRONINE (115)

B: MACRONINE (116)

C: 6A-DEOXY-8-METHOXYCRIWELLINE (117)



ABX PATTERN AND THE METHYLENEDIOXY PROTONS GIVE A SINGLET AT 6.01 P.P.M. THE METHOXYL PROTONS GIVE RISE TO A THREE PROTON SINGLET AT 3.41 P.P.M. THE TRIPLET AT 3.83 P.P.M. HAS A CHEMICAL SHIFT CHARACTERISTIC OF THE C-3 PROTON AND THE BROAD PEAK AT 2.66 P.P.M. WAS REMOVED UPON DEUTERATION THUS ESTABLISHING THE AMINO PROTON RESONANCE.

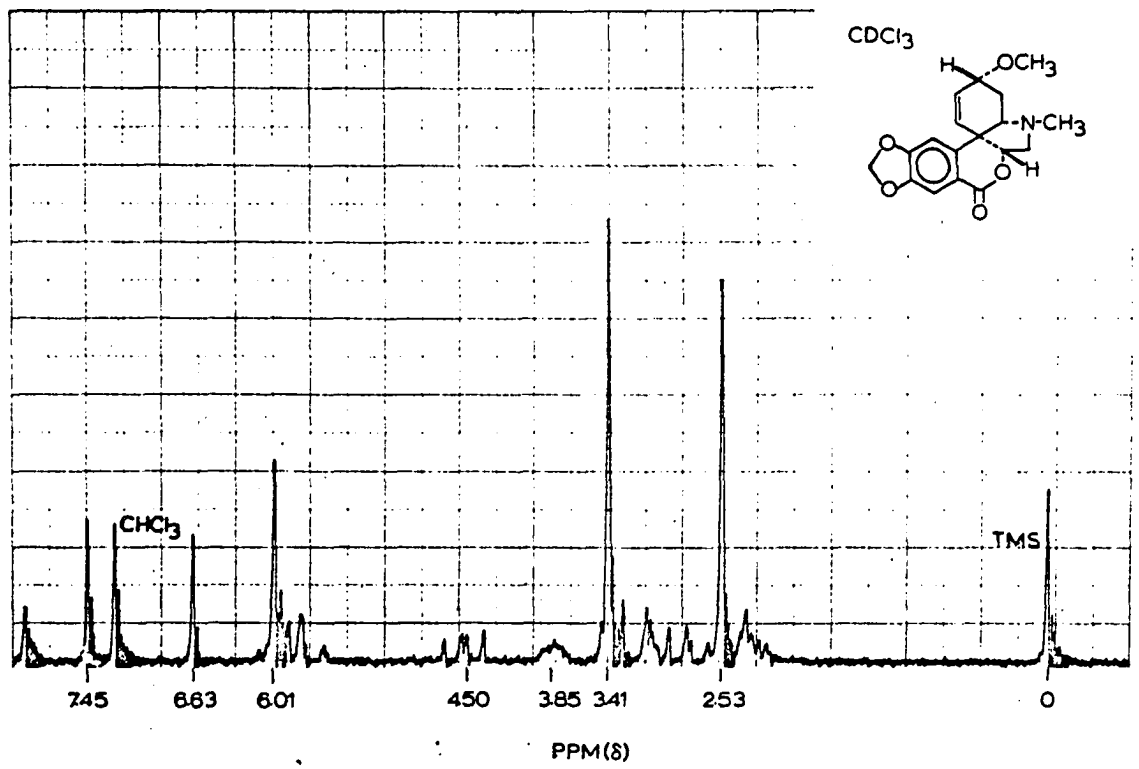
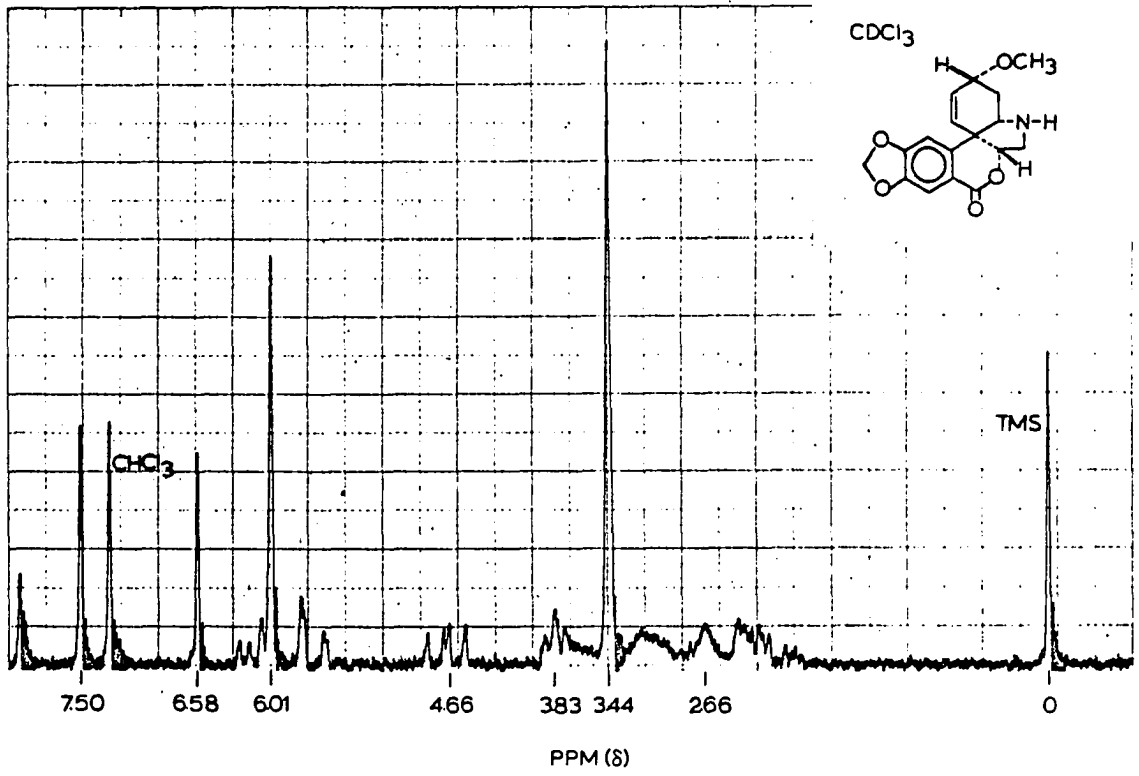
IF THE PROPOSED STRUCTURE IS CORRECT, THEN THE LACTONE 115 MUST BE THE C-6A EPIMER OF THE LACTONE 82. THE SIMILARITY OF SPECTRAL DATA SUBSTANTIATES THIS CONCLUSION. IN THE N.M.R. SPECTRA, THE C-6A PROTON IS COUPLED BY DIFFERENT COUPLING CONSTANTS TO THE C-6 PROTONS AS MIGHT BE EXPECTED FROM AN EXAMINATION OF MODELS OF THE EPIMERS. MODELS ALSO INDICATE THAT THE CONFIGURATION AT C-6A GREATLY EFFECTS THE POSITION OF THE OLEFINIC PROTONS RELATIVE TO THE AROMATIC RING, AN OBSERVATION WHICH EXPLAINS THE DIFFERENT CHEMICAL SHIFTS OBSERVED FOR THE OLEFINIC PROTONS OF THE TWO LACTONES.

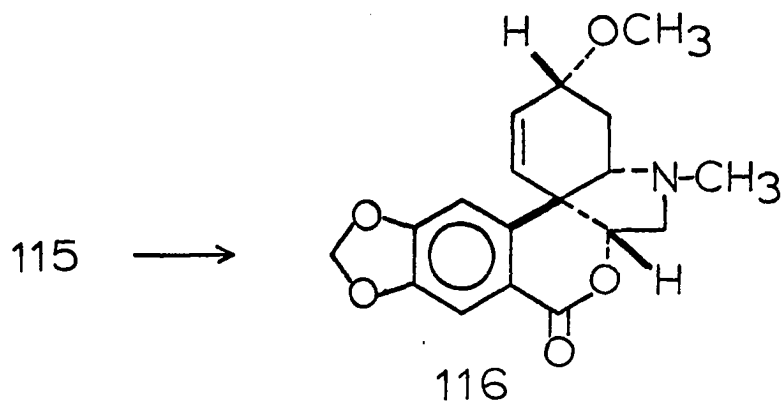
THE LACTONE (115) IS CONVERTED TO THE N-METHYL LACTONE BY CONDENSING IT WITH FORMALDEHYDE AND REDUCING THE RESULTING METHALOL WITH SODIUM BOROHYDRIDE. THIS N-METHYL LACTONE (116), M.P. 199-200⁰, SHOWED ABSORPTION IN THE INFRARED AT 5.86 AND 6.17 μ (FIG. 32B) AND IN THE ULTRAVIOLET AT 227, 267 AND 306 $m\mu$. THE N.M.R. SPECTRUM (FIG. 33B) EXHIBITED AROMATIC PROTON RESONANCES AT 6.65 AND 7.41 P.P.M. THE METHYLENEDIOXY PROTONS GIVE A SINGLET AT 6.02 P.P.M. WHICH IS SUPERIMPOSED UPON THE OLEFINIC PROTON RESONANCES (TWO OLEFINIC PROTONS WERE INDICATED BY THE SPECTRUM INTEGRAL). THE C-6A PROTON APPEARS AS A QUAR-

FIG. 33: NUCLEAR MAGNETIC RESONANCE SPECTRA

A: N-DEMETHYLMACRONINE (115)

B: MACRONINE (116)



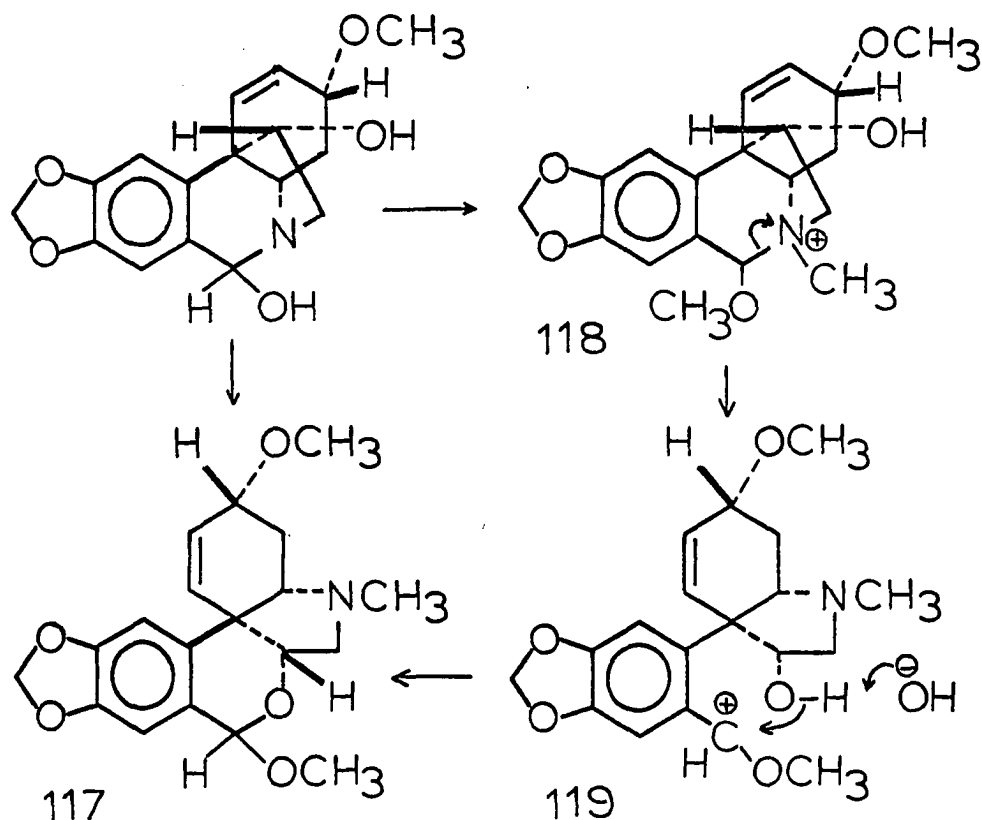


TET AT 4.8 P.P.M. AND THE TWO SINGLETS AT 3.43 AND 2.54 P.P.M. ARE ASSIGNED TO THE METHOXYL AND N-METHYL PROTONS, RESPECTIVELY. THIS LACTONE (116) WAS FOUND TO BE IDENTICAL IN ALL RESPECTS (MELTING POINT, MIXED MELTING POINT, INFRARED AND N.M.R. SPECTRA) WITH MACRONINE.

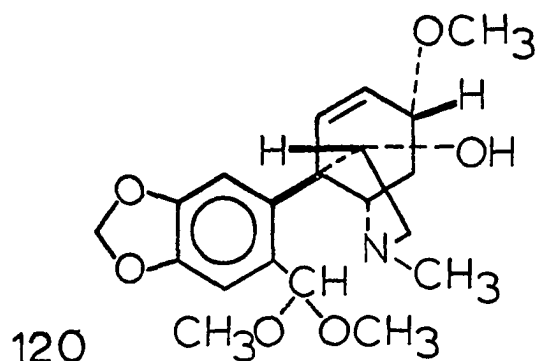
AS PREVIOUSLY NOTED, METHYLATION OF 6-HYDROXYCRINAMINE WITH METHYL IODIDE IN ACETONE GIVES 6-HYDROXYCRINAMINE METHIODIDE WHICH CAN BE CONVERTED TO CRIWELLINE WITH AQUEOUS ALKALI. HOWEVER IT WAS FOUND (D. STAUFFACHER, PRIVATE COMMUNICATION) THAT IF THE METHYLATION WAS CARRIED OUT IN REFLUXING METHANOL AND THE CORRESPONDING METHIODIDE TREATED WITH AQUEOUS ALKALI, CRIWELLINE IS NOT THE PRODUCT. THE PRODUCT OBTAINED HAS ABSORPTION IN THE ULTRAVIOLET AT 241 AND 290 $m\mu$ BUT THE INFRARED SPECTRUM (FIG. 32C) CONTAINED NO HYDROXYL OR CARBONYL ABSORPTION. THE MELTING POINT (118-119 $^{\circ}$) WAS NEAR ENOUGH TO THAT OF O-METHYLCRIWELLINE (125-126 $^{\circ}$)²⁴ TO PROMPT A COMPARISON. ALTHOUGH THE INFRARED SPECTRA OF THE TWO COMPOUNDS WERE NOT IDENTICAL, THE SIMILARITY INDICATED THAT A CLOSE RELATIONSHIP

MAY EXIST BETWEEN THE TWO COMPOUNDS. THE N.M.R. SPECTRUM OF O-METHYLCRIWELLINE IS PRESENTED IN FIG. 29B. THE AROMATIC PROTONS PRODUCE PEAKS OF NEARLY THE SAME CHEMICAL SHIFT AT 6.52 P.P.M. AND THE OLEFINIC PROTONS GIVE RISE TO A MULTIPLY IN THE 6 P.P.M. REGION. A SINGLET AT 5.89 P.P.M. IS ASSIGNED TO THE METHYLENEDIOXY PROTONS. THE NEAR SINGLET AT 4.68 P.P.M. REPRESENTS A NEARLY COLLAPSED AB PATTERN ($J_{AB} = 15$ C.P.S.) PRODUCED BY THE BENZYLIC PROTONS. THE ONE PROTON MULTIPLY AT 3.8 P.P.M. IS ASSIGNED TO THE C-3 PROTON. THE SINGLETS AT 3.41, 3.32 AND 2.40 P.P.M. ARE PRODUCED BY THE METHOXYLS AND N-METHYL, RESPECTIVELY. A COMPARISON OF THE N.M.R. SPECTRUM OF O-METHYLCRIWELLINE WITH THAT OF COMPOUND 117 (FIG. 25B) INDICATES THAT THE SIMILARITY OF PROPERTIES OF THE TWO COMPOUNDS WAS MISLEADING. THE AROMATIC PROTONS OF 117 GIVE RISE TO SINGLETS AT 6.52 AND 6.68 P.P.M., BUT THE OLEFINIC PROTONS GIVE PEAKS THAT ARE ALMOST COMPLETELY SUPERIMPOSED UPON THE METHYLENEDIOXY PROTON PEAK AT 5.82 P.P.M. THE MOST SIGNIFICANT FEATURE OF THIS SPECTRUM IS THE PRESENCE OF TWO METHOXYL PEAKS AT 3.55 AND 3.41 P.P.M. AND THE LOW FIELD SINGLET AT 5.46 P.P.M. THE N-METHYL PROTON RESONANCE APPEARS AT 2.50 P.P.M. AND THE FIVE LINE MULTIPLY AT 3.80 P.P.M. IS PROBABLY PRODUCED BY THE C-3 PROTON. THE PRESENCE OF THE LOW FIELD SINGLET AND AN ADDITIONAL METHOXYL PEAK LED TO THE ACETAL STRUCTURE SHOWN FOR 117.

THE FORMATION OF THE ACETAL PROBABLY ARISES THROUGH THE SCHEME $36 \rightarrow 118 \rightarrow 119 \rightarrow 117$. THIS MECHANISM IS BASED UPON



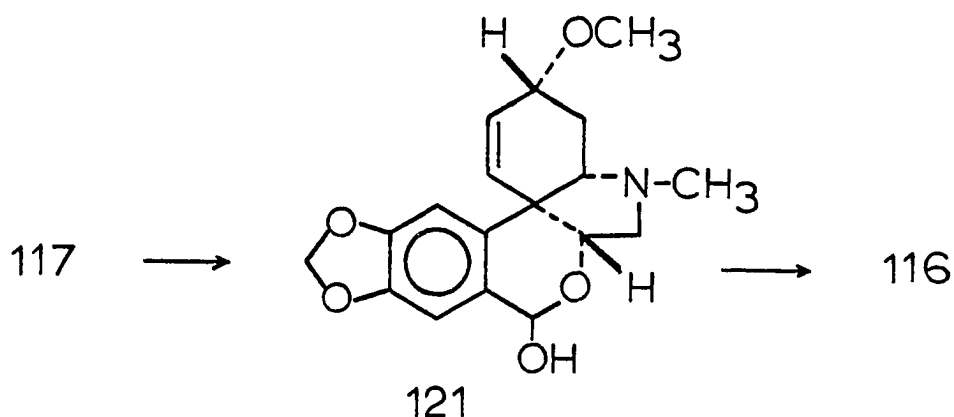
THE FOLLOWING REASONING. QUATERNIZATION OF THE NITROGEN IS APPARENTLY NECESSARY TO PROMOTE THE INCORPORATION OF THE METHOXYL GROUP AT C-6, EITHER THROUGH A DISPLACEMENT MECHANISM OR AN INTERMEDIATE ACETAL. THIS IS CONSISTENT WITH THE OBSERVATION THAT WHEN METHYL IODIDE-D₃ WAS USED AS THE METHYLATING AGENT, ONLY 117-ND₃ WAS ISOLATED (DETERMINED FROM THE N.M.R. SPECTRUM). FORMATION OF THE CARBONIUM ION 119 IS INDICATED BECAUSE INTERNAL DISPLACEMENT IS STERICALLY IMPOSSIBLE. HOWEVER THE LIFETIME OF 119 MUST BE VERY SHORT BECAUSE ONCE THE C-6-NITROGEN BOND IS BROKEN, THE C-11 HYDROXYL ANION IS AVAILABLE FOR BOND FORMATION. AN OPEN CHAIN ALTERNATIVE (120) FOR



118 MUST BE DISCOUNTED BECAUSE AN N-DIMETHYL COMPOUND WOULD BE FORMED AND THE EVIDENCE DOES NOT SUPPORT SUCH A STRUCTURE.

PROOF FOR THE STRUCTURE OF 117 WAS OBTAINED IN TWO OTHER WAYS IN ADDITION TO THE N.M.R. SPECTRUM. UPON ACID HYDROLYSIS AND BASIFICATION, THE ACETAL WAS CONVERTED TO CRIWELLINE. A LIKELY INTERMEDIATE IS THE ALDEHYDE 92, AND INTERMEDIATE IN THE CONVERSION OF 6-HYDROXYCRINAMINE TO CRIWELLINE. SECONDLY, THE ACETAL WAS CONVERTED TO THE LACTONE 116 BY TREATING IT WITH CHROMIUM TRIOXIDE IN ACETIC ACID. A PROBABLE INTERMEDIATE IN THIS REACTION IS THE HEMIACETAL 121. THE RESULTING LACTONE WAS IDENTICAL WITH MACRONINE.

IN BOTH REACTION SEQUENCES IN WHICH THE FINAL PRODUCT IS MACRONINE, ALL REACTIONS WOULD BE EXPECTED TO GIVE RETENTION OF CONFIGURATION AT C-6A. THUS MACRONINE MUST HAVE THE RELATIVE STEREOCHEMISTRY SHOWN IN STRUCTURE 116. MACRONINE BECOMES THE FIRST ALKALOID OF THE AMARYLLIDACEAE OF KNOWN STRUCTURE THAT CONTAINS A LACTONE AND THE [2]BENZOPYRANO[3,4c]INDOLE RING SYSTEM.



MASS SPECTRA OF MACRONINE AND N-DEMETHYLMACRONINE

THE MASS SPECTRUM OF MACRONINE (FIG. 34A) DISPLAYS A VERY INTENSE PEAK AT m/e 70. THE FRAGMENT PRODUCING THIS PEAK IS PROBABLY FORMED IN THE SAME MANNER AS ION 110 IN THE FRAGMENTATION OF CRIWELLINE. THE RETRO DIELS-ALDER REACTION⁶³ (122) GIVES THE ION 123 WHICH IN TURN FRAGMENTS TO GIVE THE ION 110. ALSO EVIDENT IN THE MASS SPECTRUM OF MACRONINE IS THE STRONG PEAK AT m/e 299 (124) (LOSS OF FORMALDEHYDE) AND THE PEAK AT m/e 245 (125) WHICH IS ANALAGOUS TO THE m/e 247 PEAK OF CRIWELLINE AND TAZETTINE.

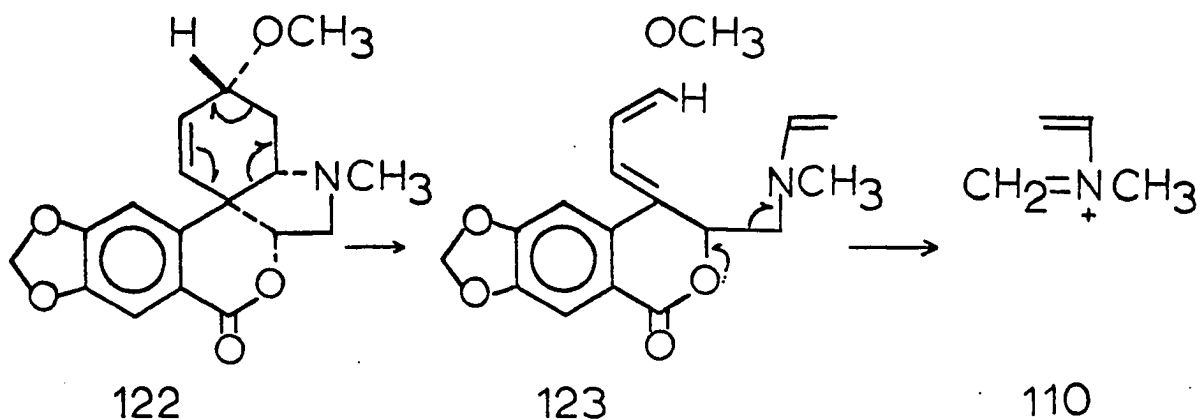
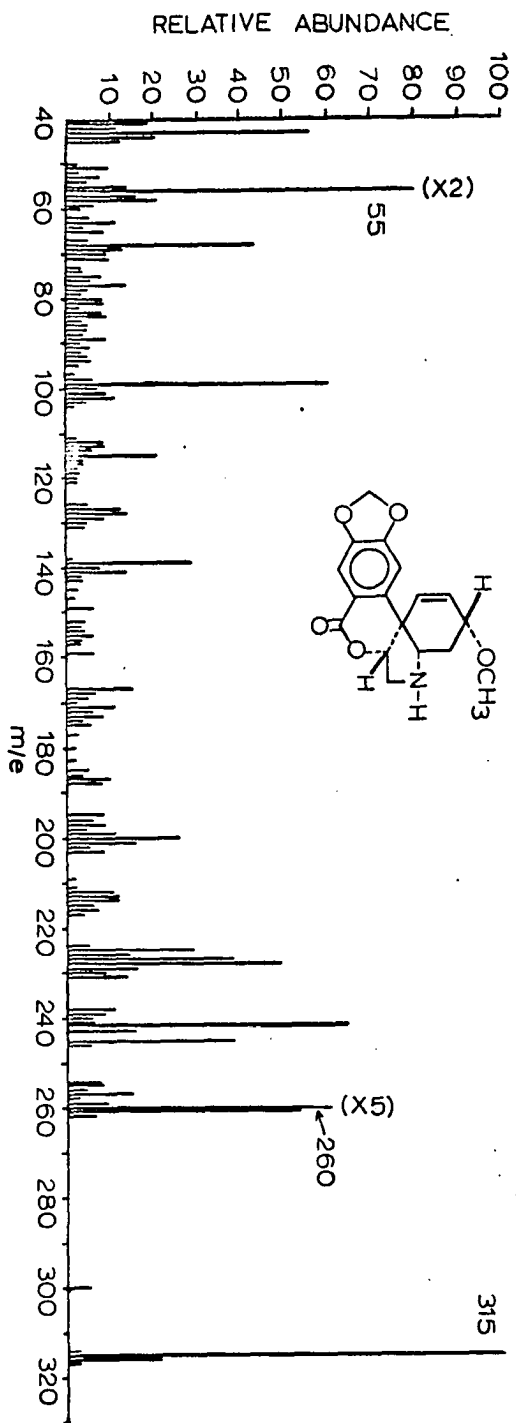
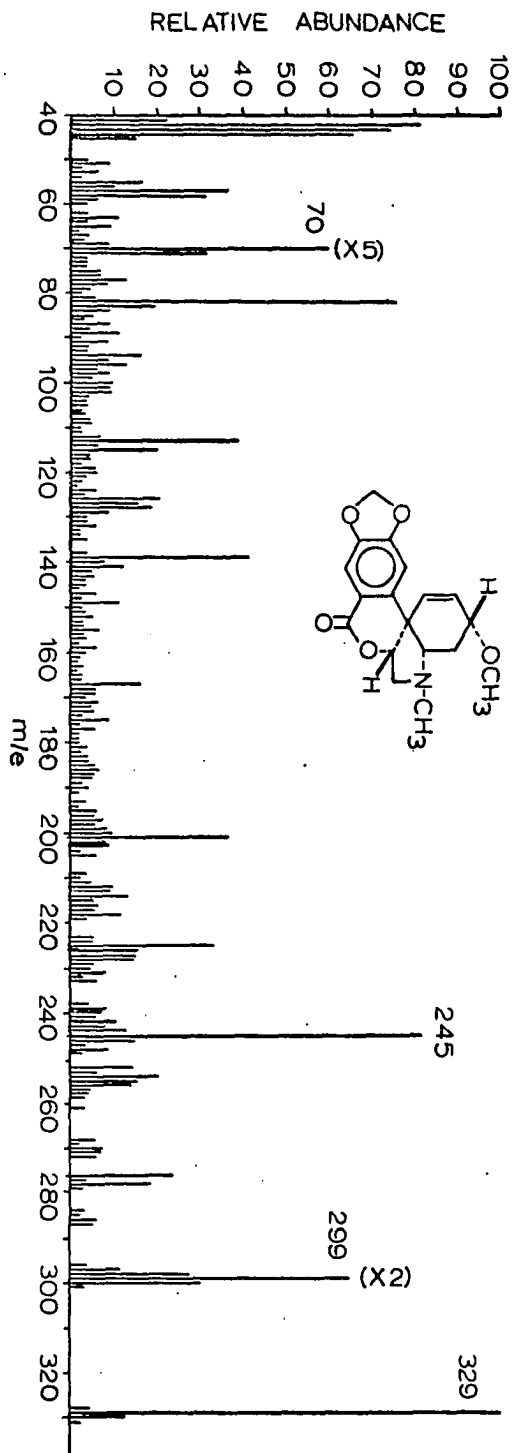


FIG. 34: MASS SPECTRA

A: MACRONINE (116)

B: N-DEMETHYLMACRONINE (115)



BIOSYNTHESIS OF CRIWELLINE

IN THE HISTORICAL SECTION OF THIS THESIS THE BIOSYNTHESIS OF TAZETTINE WAS DISCUSSED. IT WAS SUGGESTED THAT CRIWELLINE MAY BE DERIVED FROM 6-HYDROXYCRINAMINE BY A SIMILAR PATHWAY, POSSIBLY INVOLVING A HYDRIDE SHIFT AS IN THE IN VITRO CONVERSION. IT WAS DECIDED TO EXAMINE THIS POSSIBILITY BY PREPARING 6-HYDROXYCRINAMINE-11-H³ AND FEEDING THIS POTENTIAL PRECURSOR TO A PLANT CONTAINING BOTH 6-HYDROXYCRINAMINE AND CRIWELLINE. CRIWELLINE WITH TRITIUM IN THE BENZYLIC POSITION SHOULD THEN BE ISOLATED, IF THE FEEDING IS SUCCESSFUL AND THE PROPOSED PATHWAY IS CORRECT. SUBSEQUENT CHEMICAL DEGRADATION WOULD PROVE THE POSITION(S) OF RADIOACTIVITY.

AFTER STUDYING THE POSSIBLE WAYS THAT 6-HYDROXYCRINAMINE-11-H³ COULD BE PREPARED, IT WAS DECIDED THAT 6-ACETYL-11-OXOCRINAMINE (57) WOULD BE THE BEST STARTING MATERIAL. REDUCTION OF 57 WITH LITHIUM ALUMINUM HYDRIDE-H³ WOULD BE EXPECTED TO GIVE ETHANOL-1-H³ AND 6-HYDROXYCRINAMINE-11-H³. SINCE TWO FUNCTIONAL GROUPS WERE BEING REDUCED IN THE REACTION, A TRIAL EXPERIMENT WITH LITHIUM ALUMINUM DEUTERIDE AS THE REDUCING AGENT WAS PERFORMED TO DETERMINE THE AMOUNT OF ISOTOPE SUBSTITUTION AT THE C-11 POSITION.

THUS 0.10 MMOLES OF 6-ACETYL-11-OXOCRINAMINE WAS TREATED WITH 0.31 MMOLES OF LITHIUM ALUMINUM DEUTERIDE AND THEN WITH 5.3 MMOLES OF LITHIUM ALUMINUM HYDRIDE TO INSURE COMPLETE REDUCTION. THE 6-HYDROXYCRINAMINE-11-D WAS ISOLATED, PURIFIED AND EXAMINED IN THE MASS SPECTROMETER FOR ISOTOPIC PURITY.

IT WAS FOUND THAT THE P+1 PEAK OF THE DEUTERATED COMPOUND WAS 66.0% OF THE PARENT ION INTENSITY. WITH NO DEUTERIUM PRESENT THIS PEAK (P+1) THEORETICALLY SHOULD BE 19.4% OF THE PARENT ION INTENSITY, AND EXPERIMENTALLY A VALUE OF 17.2% WAS FOUND WITH 6-HYDROXYCRINAMINE. THESE RESULTS SHOW THAT 33% OF THE 6-HYDROXYCRINAMINE ISOLATED CONTAINED ONE DEUTERIUM, PRESUMABLY AT THE C-11 POSITION. ANALOGOUS RESULTS WITH 25 MILLICURIES OF LITHIUM ALUMINUM HYDRIDE- H^3 WOULD GIVE ABOUT 8 MILLICURIES OF RADIOACTIVE 6-HYDROXYCRINAMINE, OR A QUANTITY SUFFICIENTLY RADIOACTIVE TO SERVE AS A BIOSYNTHETIC PRECURSOR.

HOWEVER, THE REDUCTION OF 0.10 MMOLES OF 57 WITH 0.315 MMOLES OF LITHIUM ALUMINUM HYDRIDE- H^3 GAVE 0.22 MMOLES OF PURE 6-HYDROXYCRINAMINE-11- H^3 CONTAINING 3.6 MILLICURIES OF RADIOACTIVITY (3.92×10^{10} DPM/MMOLE). THIS MATERIAL WAS DILUTED BY A FACTOR OF TEN THOUSAND FOR DEGRADATIVE STUDIES.

THE POSITION OF THE SUBSTITUTED TRITIUM WAS PROVEN BY THE OXIDATION OF 6-HYDROXYCRINAMINE-11- H^3 (3.92×10^6 DPM/MMOLE) WITH ACETIC ANHYDRIDE IN DIMETHYLSULFOXIDE TO GIVE 6-ACETYL-11-OXOCRINAMINE. THE KETO ACETATE CONTAINED A RELATIVELY SMALL AMOUNT OF RADIOACTIVITY (2.15×10^5 DPM/MMOLE) OR 5.46% OF THE ORIGINAL ACTIVITY. THUS 94.5% OF THE RADIOACTIVITY IS SUBSTITUTED AT THE C-11 POSITION.

6-HYDROXYCRINAMINE-11- H^3 (3.92×10^6 DPM/MMOLE) WAS CONVERTED TO CRIWELLINE IN THE USUAL MANNER. THE CRIWELLINE-8- H^3 WAS ISOLATED AND FOUND TO CONTAIN 2.99×10^6 DPM/MMOLE OR 76% OF THE ACTIVITY OF THE STARTING MATERIAL. THIS INCOMPLETE

TRANSFER OF TRITIUM IS IN AGREEMENT WITH THE PREVIOUSLY NOTED INCOMPLETE TRANSFER OF DEUTERIUM IN THE SAME REACTION. A CONSIDERATION OF THIS PROBLEM LED TO FOUR POSSIBLE EXPLANATIONS FOR THE INCOMPLETE TRANSFER OF THE ISOTOPE IN THE REACTION. THESE EXPLANATIONS ARE: 6-HYDROXYCRINAMINE UNDERGOES C-11 PROTON EXCHANGE DURING THE REACTION; THE INTERMEDIATE BENZYL ALCOHOL UNDERGOES PROTON EXCHANGE DURING THE REACTION; THE BENZYLIC PROTONS OF CRIWELLINE ARE LABILE IN BASIC SOLUTION; OR THE HYDRIDE SHIFT MECHANISM IS NOT THE ONLY EXPLANATION FOR THE 6-HYDROXYCRINAMINE-CRIWELLINE CONVERSION. THE FIRST THREE ALTERNATIVES WERE TESTED EXPERIMENTALLY AS FOLLOWS.

THE POSSIBILITY OF THE C-11 PROTON OF 6-HYDROXYCRINAMINE UNDERGOING EXCHANGE IN BASIC SOLUTION WAS ELIMINATED. 6-HYDROXYCRINAMINE-11-H³ (3.87 X 10⁶ DPM/MMOLE) WAS SHAKEN WITH BOTH 1 N HYDROCHLORIC ACID AND 1 N SODIUM HYDROXIDE SOLUTION AND ALLOWED TO STAND IN THE LATTER SOLUTION FOR FIVE MINUTES. THE 6-HYDROXYCRINAMINE-11-H³ WAS ISOLATED, PURIFIED AND ITS RADIOACTIVITY DETERMINED AS 3.95 X 10⁶ DPM/MMOLE. THIS RESULT SHOWS THAT NO EXCHANGE OCCURRED UNDER CONDITIONS SIMILAR TO THOSE USED TO EFFECT THE REARRANGEMENT.

A SIMILAR EXPERIMENT WAS CARRIED OUT WITH CRIWELLINE-8-H³ TO TEST THE LABILITY OF THE BENZYLIC PROTONS. CRIWELLINE-8-H³ (2.99 X 10⁶ DPM/MMOLE) WAS DISSOLVED IN 1 N HYDROCHLORIC ACID AND MADE BASIC TO ABOUT 1 N WITH SODIUM HYDROXIDE AND THE SOLUTION WAS ALLOWED TO STAND FOR 15 MINUTES. THE ALKALOID WAS ISOLATED AND PURIFIED IN THE USUAL MANNER AND ITS RADIOACTIVITY

DETERMINED AS 2.92×10^6 DPM/MMOLE. AGAIN IT IS CONCLUDED THAT NO EXCHANGE OCCURRED.

THE POSSIBILITY OF PROTON EXCHANGE OCCURRING WITH THE BENZYL ALCOHOL INTERMEDIATE WAS INVESTIGATED INDIRECTLY. TAZETTADIOL (5) IS AN ALCOHOL OF SIMILAR STRUCTURE AND WAS THE COMPOUND USED FOR THIS EXPERIMENT. TAZETTADIOL WAS DISSOLVED IN DIOXANE AND ADDED TO A SOLUTION OF 1 N SODIUM DEUTEROXIDE IN DEUTERIUM OXIDE AND THE MIXTURE WAS ALLOWED TO STAND FOR 30 MINUTES. THE SOLUTION WAS EXTRACTED WITH CHLOROFORM AND THE TAZETTADIOL ISOLATED. THE N.M.R. SPECTRUM SHOWED THAT ESSENTIALLY NO DEUTERIUM HAD BEEN INCORPORATED IN THE BENZYLIC POSITION. THIS EXPERIMENT SUGGEST THAT NO EXCHANGE OCCURRED WITH THE BENZYL ALCOHOL INTERMEDIATE.

TWO OTHER EXPERIMENTS WERE PERFORMED TO HELP ESTABLISH THE POINT AT WHICH THE TRITIUM WAS LOST. IN THE FIRST EXPERIMENT, 6-HYDROXYCRINAMINE-11- H^3 (4.70×10^6 DPM/MMOLE) WAS CONVERTED TO ITS METHIODIDE IN THE USUAL WAY AND THE METHIODIDE WAS ISOLATED. THE METHIODIDE WAS RECRYSTALLIZED AS A DIHYDRATE AND ITS RADIOACTIVITY DETERMINED AS 4.54×10^6 DPM/MMOLE. WITHIN EXPERIMENTAL ERROR, ALL OF THE RADIOACTIVITY IS RETAINED IN THE PREPARATION OF THE METHIODIDE.

IN ANOTHER EXPERIMENT, THE BASIC SOLUTION USED TO EFFECT THE REARRANGEMENT OF 6-HYDROXYCRINAMINE (1.25×10^4 DPM/MG., 152 MG.) WAS EXAMINED FOR RADIOACTIVITY. THE AQUEOUS SOLUTION GAVE A NEGATIVE ALKALOID TEST WITH SILICOTUNGSTIC ACID AND CONTAINED 5000 DPM/ML. OR A TOTAL OF 1.6×10^5 DPM. THIS

AMOUNT OF RADIOACTIVITY IS 8.5% OF THAT OF THE STARTING MATERIAL. THE CRIWELLINE-8-H³ ISOLATED FROM THE EXPERIMENT WEIGHED 161 MG. (THEORETICAL = 160 MG.) AND CONTAINED A TOTAL OF 1.46 X 10⁶ DPM/160 MG. OR 76% OF THE ORIGINAL ACTIVITY OF THE 6-HYDROXYCRINAMINE-11-H³. ABOUT ONE-THIRD OF THE MISSING RADIOACTIVITY WAS IN THE BASIC SOLUTION AND THE REMAINING TWO-THIRDS IS UNACCOUNTED FOR. THE EVIDENCE PRESENTED INDICATES THAT SOME MECHANISM IN ADDITION TO THE HYDRIDE SHIFT PROPOSAL MUST BE EFFECTIVE IN THE CONVERSION OF 6-HYDROXYCRINAMINE TO CRIWELLINE.

TO EXAMINE THE METHOD OF DEGRADATION OF RADIOACTIVE CRIWELLINE, SOME CRIWELLINE-8-H³ WAS DEGRADED COMPLETELY. CRIWELLINE-8-H³ (2.00 X 10⁶ DPM/MMOLE) WAS METHYLATED WITH METHYL IODIDE AND SUBJECTED TO HOFMANN DEGRADATIVE CONDITIONS. THE METHINE WAS ISOLATED AND PURIFIED BY DISTILLATION. ALL OF THE RADIOACTIVITY WAS RETAINED IN THE METHINE (2.02 X 10⁶ DPM/MMOLE). THE METHINE WAS SUBJECTED TO METHANOLYSIS TO GIVE 6-PHENYLPIPERONYL ALCOHOL. THE ALCOHOL WAS SUBLIMED AND ITS RADIOACTIVITY DETERMINED AS 2.04 X 10⁶ DPM/MMOLE. AGAIN ALL OF THE RADIOACTIVITY WAS RETAINED. THE 6-PHENYLPIPERONYL ALCOHOL (2.04 X 10⁶ DPM/MMOLE) WAS OXIDIZED WITH A NEUTRAL PERMANGANATE SOLUTION TO 6-PHENYLPIPERONYLIC ACID. THE SUBLIMED ACID CONTAINED 6.72 X 10⁴ DPM/MMOLE OR 3.30% OF THE ACTIVITY OF THE ALCOHOL. THUS 97% OF THE RADIOACTIVITY OF CRIWELLINE-8-H³ IS IN THE BENZYLIC POSITION. ALL THE DEGRADATIVE EVIDENCE IS SUMMARIZED IN TABLE 3 AND FIG. 35.

TABLE 3. DEGRADATION OF 6-HYDROXYCRINAMINE-11-H³

COMPOUND	RELATIVE RADIOACTIVITY
6-HYDROXYCRINAMINE	1.00
6-HYDROXYCRINAMINE (ACID-BASE EQUIL.)	1.02
6-ACETYL-11-OXOCRINAMINE	0.06
6-HYDROXYCRINAMINE METHIODIDE	0.97
AQUEOUS BASE SOLUTION	0.08
CRIWELLINE	0.76
CRIWELLINE (ACID-BASE EQUIL.)	0.74
HOFMANN METHINE	0.77
6-PHENYLPUPERONYL ALCOHOL	0.77
6-PHENYLPUPERONYLIC ACID	0.02

THE PREVIOUSLY OUTLINED DEGRADATION IS A POSSIBLE SCHEME BY WHICH RADIOACTIVE CRIWELLINE MAY BE DEGRADED. THE IMPORTANT ASPECT OF THE DEGRADATION IS THAT NO TRITIUM IS LOST UNTIL THE 6-PHENYLPUPERONYL ALCOHOL IS OXIDIZED.

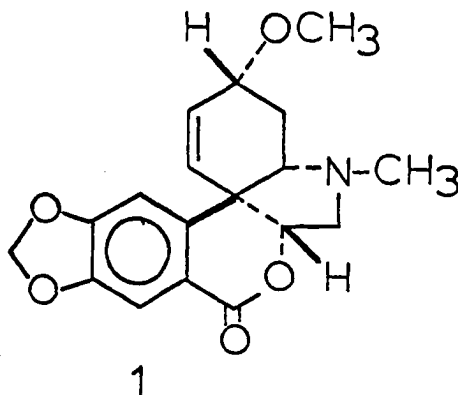
THE ACTUAL FEEDING EXPERIMENT IS NOT INCLUDED IN THIS THESIS. AT THE TIME OF THIS WRITING A SUITABLE PLANT HAS NOT BEEN OBTAINED FOR THE IN VIVO STUDIES. IT WAS ORIGINALLY HOPED THAT C. ERUBESCENS COULD BE USED FOR THE IN VIVO STUDIES, HOWEVER THE YIELDS OF CRIWELLINE FROM THIS PLANT ARE LOW AND ERRATIC, MAKING IT AN UNSATISFACTORY SOURCE.

SUMMARY

CHEMICAL AND SPECTRAL PROPERTIES OF 6-HYDROXYCRINAMINE AND RELATED COMPOUNDS HAVE BEEN STUDIED. THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF 6-HYDROXYCRINAMINE AND HAEMANTHIDINE SHOW THAT THE C-6 PROTON OF THESE ALKALOIDS HAS TWO CHEMICAL SHIFTS. FURTHER INVESTIGATIONS UTILIZING SOLVENT EFFECTS AND VARIABLE TEMPERATURE STUDIES HAVE SHOWN THAT ALL 6-HYDROXY-5,10B-ETHANO-PHENANTHRIDINE ALKALOIDS EXIST IN SOLUTION AS AN EQUILIBRATING MIXTURE OF EPIMERS. AN INTERPRETATION OF THIS PHENOMENON AS WELL AS SPECTRAL DATA IS PRESENTED.

THE MASS SPECTRA OF 6-HYDROXYCRINAMINE, HAEMANTHIDINE, CRIWELLINE, TAZETTINE AND MACRONINE ARE PRESENTED. DEUTERIUM LABELING WAS USED TO ASSIST IN ASSIGNING POSSIBLE STRUCTURES TO THE IONS FORMED DURING FRAGMENTATION.

6-HYDROXYCRINAMINE WAS CONVERTED BY TWO DIFFERENT ROUTES TO MACRONINE, AN ALKALOID OF PREVIOUSLY UNKNOWN STRUCTURE. MACRONINE WAS SHOWN TO HAVE THE STRUCTURE 1.



THE MECHANISM OF THE 6-HYDROXYCRINAMINE-CRIWELLINE REARRANGEMENT HAS BEEN EXTENSIVELY STUDIED WITH DEUTERIUM AND TRITIUM LABELING. THE EVIDENCE INDICATES THAT 76% OF THE REARRANGEMENT CAN BE EXPLAINED BY A HYDRIDE SHIFT MECHANISM BUT THE REMAINING 24% REQUIRES AN ALTERNATIVE MECHANISM.

6-HYDROXYCRINAMINE-11-H³ WAS SYNTHESIZED FOR THE PURPOSE OF STUDYING THE IN VIVO CONVERSION OF 6-HYDROXYCRINAMINE TO CRIWELLINE. A DEGRADATIVE SCHEME IS OUTLINED FOR THE RADIOACTIVE CRIWELLINE.

EXPERIMENTAL

THE N.M.R. SPECTRA CITED IN THIS THESIS WERE OBTAINED WITH EITHER A VARIAN A-60 OR HR-60 SPECTROMETER OPERATING AT 60 MC.P.S. SPIN DECOUPLING EXPERIMENTS WERE PERFORMED BY A MODIFICATION OF THE METHOD OF JOHNSON.³⁹ THE MASS SPECTRA WERE OBTAINED WITH AN ATLAS CH-4 MASS SPECTROMETER AND THE HIGH RESOLUTION MEASUREMENTS WERE DONE ON AN A.E.I. MS-9 DOUBLE FOCUSING MASS SPECTROMETER. MELTING POINTS WERE TAKEN ON A KOFLER MICROSCOPE HOT STAGE AND ARE CORRECTED. OPTICAL ROTATIONS WERE OBSERVED IN 95% ETHANOL ON A JASCO MODEL ORD/UV 5 RECORDING SPECTROPOLARIMETER. ULTRAVIOLET SPECTRA WERE OBTAINED WITH A BECKMAN DK 2 ULTRAVIOLET-VISIBLE SPECTROPHOTOMETER AND THE INFRARED SPECTRA WERE OBTAINED ON A PERKIN ELMER MODEL 21 INFRARED SPECTROPHOTOMETER.

THE PREPARATIONS OF THE FOLLOWING COMPOUNDS HAVE BEEN CITED IN THE LITERATURE AND AN ANALAGOUS PROCEDURE WAS USED IN THEIR PREPARATIONS FOR STUDIES DESCRIBED HEREIN: TAZETTADIOL, ISOTAZETTINOL, DIHYDROTAZETTINE, CRIWELLAMIDE, APOHAEMANTHIDINE, AND O-METHYLCRIWELLINE. ALL OF THESE COMPOUNDS HAVE PHYSICAL PROPERTIES IN AGREEMENT WITH THOSE REPORTED.^{10, 17}

ISOLATION OF ALKALOIDS

ALKALOIDS FROM CRINUM ERUBESCENS

CRINUM ERUBESCENS (14.5 KG.) WAS FINELY GROUND AND SUSPENDED IN ABOUT 20 L. OF 95% ETHANOL CONTAINING 200 G. OF TAR-

TARIO ACID. AFTER THREE DAYS THE PLANT MATERIAL WAS FILTERED AND THE FILTRATES WERE CONCENTRATED UNDER REDUCED PRESSURE. THIS PROCESS WAS REPEATED THREE MORE TIMES. THE CONCENTRATED FILTRATES WERE DILUTED TO THREE TIMES THE ORIGINAL VOLUME WITH WATER AND MADE ACIDIC (PH 1) WITH HYDROCHLORIC ACID. ACTIVATED CHARCOAL WAS ADDED AND THE SUSPENSION WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 24 HOURS AND THEN FILTERED THROUGH CELITE. THE ACIDIC SOLUTION WAS EXTRACTED WITH CHLOROFORM AND THE CHLOROFORM WAS EVAPORATED TO DRYNESS TO GIVE ABOUT 1 G. OF MATERIAL. THE FREE BASES WERE REGENERATED FROM THE HYDROCHLORIDES BY AQUEOUS AMMONIA SOLUTION AND EXTRACTED WITH CHLOROFORM. A THIN LAYER CHROMATOGRAM OF THE ALKALOID MIXTURE SHOWED THAT THE MIXTURE WAS MAINLY 6-HYDROXYCRINAMINE AND IT WAS ADDED TO THE BASIC EXTRACT DESCRIBED BELOW. THE ABOVE ACIDIC SOLUTION WAS MADE BASIC WITH 20% SODIUM HYDROXIDE (TO PH 11) AND EXTRACTED WITH ETHANOL-CHLOROFORM MIXTURES UNTIL A NEGATIVE ALKALOID TEST (SILICOTUNGSTIC ACID) WAS OBTAINED. THE EXTRACTS WERE CONCENTRATED TO DRYNESS AND THEN SUSPENDED IN CHLOROFORM. THE SUSPENSION WAS FILTERED TO GIVE 21.6 G. OF LYCORINE (IDENTIFIED BY ITS INFRARED SPECTRUM). THE FILTRATES WERE CONCENTRATED TO DRYNESS TO YIELD 58 G. OF CRUDE ALKALOID EXTRACT. THE EXTRACT WAS CHROMATOGRAPHED ON 1100 G. OF BASIC ALUMINA (MEROK). THE 100% CHLOROFORM FRACTION YIELDED 0.60 G. OF NON-ALKALOIDAL MATERIAL WHICH WAS NOT IDENTIFIED FURTHER. ELUTION WITH 2:98 METHANOL:CHLOROFORM GAVE A MIXTURE OF CRINAMINE AND 6-HYDROXYCRINAMINE (T.L.C.). THIS MIXTURE WAS RECHRO-

MATOGRAPHED OVER FLORISIL TO GIVE 1.4 G. OF CRINAMINE. 6-HYDROXYCRINAMINE WAS ELUTED FROM BOTH COLUMNS WITH 4-8% METHANOL IN CHLOROFORM. THE TOTAL WEIGHT OF 6-HYDROXYCRINAMINE ISOLATED WAS 24.5 G. ELUTION WITH 10% METHANOL IN CHLOROFORM GAVE 0.82 G. OF CRIWELLINE. ELUTION WITH 10-20% METHANOL IN CHLOROFORM GAVE SOME RESIDUAL LYCORINE (IDENTIFIED BY T.L.C.) AND 1.5 G. OF CORANICINE (INFRARED SPECTRUM). THE ALKALOID CONTENT OF THE PLANT MATERIAL IS LISTED IN THE FOLLOWING TABLE.

TABLE 4. ALKALOIDS OF CRINUM ERUBESCENS

ALKALOID	WEIGHT	% OF WET PLANT MATERIAL
CRINAMINE	1.4 G.	0.01
6-HYDROXYCRINAMINE	24.5 G.	0.17
CRIWELLINE	0.82 G.	0.005
LYCORINE	21.6 G.	0.15
CORANICINE	1.5 G.	0.01

PREPARATION OF DERIVATIVES

DIACETYL-6-HYDROXYCRINAMINE (42)

A SOLUTION OF 0.600 G. OF 6-HYDROXYCRINAMINE IN 5 ML. OF PYRIDINE WAS TREATED WITH 5 ML. OF ACETIC ANHYDRIDE AND ALLOWED TO STAND AT ROOM TEMPERATURE FOR 28 HOURS. THE EXCESS PYRIDINE AND ACETIC ANHYDRIDE WERE REMOVED UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN BENZENE AND CHROMATOGRAPHED ON 40 G. OF BASIC ALUMINA (MERCK). ELUTION WITH 1% ETHYL ACETATE IN BENZENE GAVE 0.120 G. OF 6,11-DIACETYL-6-HY-

DROXYCRINAMINE. ELUTION WITH CHLOROFORM GAVE 0.320 G. OF 11-ACETYL-6-HYDROXYCRINAMINE. DIACETYL-6-HYDROXYCRINAMINE MAY BE PURIFIED BY DISTILLATION (0.001 MM., 120°) WHICH GIVES A SOLID: M.P. $95-97^{\circ}$; $[\alpha]_{589}^{25} +21^{\circ}$, $[\alpha]_{436}^{25} +67^{\circ}$; $\lambda_{\text{MAX}}^{\text{KBR}} 5.76 \mu$; $\lambda_{\text{MAX}}^{\text{ETOH}} 241 \mu$ (ϵ 4200) AND 291μ (ϵ 4800). THE N.M.R. SPECTRUM OF 6,11-DIACETYL-6-HYDROXYCRINAMINE IS SHOWN IN FIG. 7A AND DISCUSSED ON PAGE 45.

ANAL. CALCD. FOR $\text{C}_{21}\text{H}_{23}\text{NO}_7$: C, 62.83; H, 5.78; N, 3.49. —
 FOUND: C, 62.76; H, 5.77; N, 3.63.

11-ACETYL-6-HYDROXYCRINAMINE (44)

THE 11-ACETYL-6-HYDROXYCRINAMINE OBTAINED ABOVE WAS PURIFIED BY RECRYSTALLIZATION FROM ETHYL ACETATE: M.P. $134-135^{\circ}$; $[\alpha]_{589}^{25} +49^{\circ}$, $[\alpha]_{436}^{25} +139^{\circ}$ (c 0.42); $\lambda_{\text{MAX}}^{\text{KBR}} 5.76 \mu$ (FIG. 3A); $\lambda_{\text{MAX}}^{\text{ETOH}} 240 \mu$ (ϵ 3600) AND 290μ (ϵ 4500). THE N.M.R. SPECTRUM OF 44 IS SHOWN IN FIG. 11A AND DISCUSSED ON PAGE 56.

ANAL. CALCD. FOR $\text{C}_{19}\text{H}_{21}\text{NO}_6$: C, 63.50; H, 5.89; N, 3.90.
 FOUND: C, 63.42; H, 6.15; N, 3.89.

11-ACETYL-6-OXOCRINAMINE (45)

A SOLUTION OF 0.220 G. OF 11-ACETYL-6-HYDROXYCRINAMINE IN 30 ML. OF CHLOROFORM CONTAINING 1.00 G. OF ACTIVATED MANGANESE DIOXIDE WAS STIRRED AT ROOM TEMPERATURE FOR 20 HOURS. THE MANGANESE DIOXIDE WAS REMOVED BY FILTRATION AND THE FILTRATE WAS CONCENTRATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.195 G. OF RESIDUE. THE RESIDUE WAS CHROMATOGRAPHED ON 15 G. OF ALUMINA TO GIVE IN 5% METHANOL IN CHLOROFORM, 0.150 G. 11-

ACETYL-6-OXOCRINAMINE. THE LACTAM WAS RECRYSTALLIZED FROM ETHYL ACETATE TO GIVE NEEDLES: M.P. 88-91°; $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.75 μ AND 5.88 μ (FIG. 3B); $\lambda_{\text{MAX}}^{\text{ETOH}}$ 232 m μ (ϵ 26,000), 274 m μ (ϵ 6500) AND 321 m μ (ϵ 5900).

ANAL. CALCD. FOR $\text{C}_{19}\text{H}_{19}\text{NO}_6$: C, 63.86; H, 5.36; N, 3.92.
FOUND: C, 63.46; H, 5.50; N, 3.87.

6,11-DIACETYLDIHYDRO-6-HYDROXYCRINAMINE (46)

A SOLUTION OF 0.400 G. OF DIHYDRO-6-HYDROXYCRINAMINE IN 10 ML. OF ACETYLATED REAGENT ⁶⁴ WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 30 MINUTES. THE SOLUTION WAS COOLED IN AN ICE BATH AND MADE BASIC (PH 9) WITH 20% SODIUM HYDROXIDE SOLUTION. THE SOLUTION WAS DILUTED WITH 50 ML. OF WATER AND EXTRACTED TWICE WITH ETHYL ACETATE. THE EXTRACT WAS DRIED OVER ANHYDROUS SODIUM SULFATE AND THE ETHYL ACETATE REMOVED UNDER REDUCED PRESSURE. THE GUM (0.450 G.) WAS CHROMATOGRAPHED ON 25 G. OF FLORISIL. ELUTION WITH 1% ETHYL ACETATE IN BENZENE GAVE 0.410 G. OF DIACETYLDIHYDRO-6-HYDROXYCRINAMINE WHICH RESISTED ALL ATTEMPTS AT CRYSTALLIZATION. THE SUBLIMED GLASS SHOWED: $[\alpha]_{589}^{25} +73^\circ$, $[\alpha]_{436}^{25} +204^\circ$ (C 0.66); $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.75 μ (FIG. 3C); $\lambda_{\text{MAX}}^{\text{ETOH}}$ 239 m μ (ϵ 5300) AND 290 m μ (ϵ 5700). THE N.M.R. SPECTRUM OF 46 IS SHOWN IN FIG. 9A AND DISCUSSED ON PAGE 48.

ANAL. CALCD. FOR $\text{C}_{21}\text{H}_{25}\text{NO}_7$: C, 62.52; H, 6.25; N, 3.47.
FOUND: C, 62.48; H, 6.26; N, 3.40.

6,11-DIACETYLDIHYDROHAEMANTHIDINE (47)

BY THE PROCEDURE CITED FOR THE PREPARATION OF 50, 0.245 G. OF DIHYDROHAEMANTHIDINE WAS CONVERTED TO 0.200 G. OF CRUDE DIACETATE. THE PRODUCT WAS RECRYSTALLIZED FROM ACETONE-ETHER: M.P. 246-248°; $[\alpha]_{589}^{25} +39^{\circ}$, $[\alpha]_{436}^{25} +76^{\circ}$ (c 0.51); $\lambda_{\text{MAX}}^{\text{KBR}} 5.74\mu$ (FIG. 4A); $\lambda_{\text{MAX}}^{\text{ETOH}} 238 \text{ m}\mu$ (ϵ 3900) AND 289 $\text{m}\mu$ (ϵ 3900). THE N.M.R. SPECTRUM OF 47 IS SHOWN IN FIG. 9B AND DISCUSSED ON PAGE 48.

ANAL. CALCD. FOR $\text{C}_{21}\text{H}_{25}\text{NO}_7$: C, 62.52; H, 6.25; N, 3.47.
 FOUND: C, 62.35; H, 6.23; N, 3.42.

11-ACETYLDIHYDRO-6-HYDROXYCRINAMINE (48)

A SOLUTION OF 0.350 G. OF DIACETYL-6-HYDROXYCRINAMINE IN 10 ML. OF GLACIAL ACETIC ACID WAS HYDROGENATED AT ROOM TEMPERATURE AND ATMOSPHERIC PRESSURE WITH 0.100 G. OF PLATINUM OXIDE. THE REACTION STOPPED AFTER THE UPTAKE OF 1 EQUIV. OF HYDROGEN. THE CATALYST WAS REMOVED BY FILTRATION AND THE SOLVENT REMOVED UNDER REDUCED PRESSURE. THE RESIDUE (0.348 G.) WAS CHROMATOGRAPHED ON 20 G. OF ALUMINA. ELUTION WITH SOLVENTS RANGING FROM 10% ETHYL ACETATE IN BENZENE THROUGH 10% METHANOL IN CHLOROFORM GAVE 0.190 G. OF 52 WHICH WAS RECRYSTALLIZED FROM ACETONE ETHER AND SUBLIMED FOR ANALYSIS: M.P. 217-218°; $[\alpha]_{589}^{25} +168^{\circ}$, $[\alpha]_{436}^{25} +316^{\circ}$ (c 0.11); $\lambda_{\text{MAX}}^{\text{KBR}} 5.74\mu$ (FIG. 4B); $\lambda_{\text{MAX}}^{\text{ETOH}} 237 \text{ m}\mu$ (ϵ 4400) AND 288 $\text{m}\mu$ (ϵ 5300). THE N.M.R. SPECTRUM OF 48 IS SHOWN IN FIG. 11B AND DISCUSSED ON PAGE 56.

ANAL. CALCD. FOR $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88.

FOUND: C, 63.06; H, 6.18; N, 3.88.

6,11-DIOXOCRINAMINE (55)

PROCEDURE A A SOLUTION OF 0.120 G. OF CHROMIUM TRIOXIDE IN 10 ML. OF DIMETHYLFORMAMIDE WAS STIRRED UNTIL THE CHROMIUM TRIOXIDE WAS DISSOLVED. 6-OXOCRINAMINE (0.120 G.) WAS ADDED AND THE SOLUTION WAS STIRRED WHILE ONE DROP OF CONCENTRATED SULFURIC ACID WAS ADDED. THE SOLUTION WAS STIRRED FOR 24 HOURS AT ROOM TEMPERATURE. THE SOLUTION WAS DILUTED TO ABOUT 250 ML. WITH WATER AND EXTRACTED FOUR TIMES WITH BENZENE, AND THE BENZENE SOLUTION WASHED THREE TIMES WITH WATER. THE ORGANIC SOLUTION WAS FILTERED THROUGH COTTON AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE POWDERY RESIDUE (0.048 G.) WAS FOUND TO BE NEARLY PURE BY T.L.C. AND WAS CRYSTALLIZED FROM ACETONE-ETHER: M.P. 199-200⁰; $[\alpha]_{589}^{25} +180^{\circ}$, $[\alpha]_{436}^{25} +770^{\circ}$; $\lambda_{MAX}^{KBR} 5.73 \mu$ AND 5.90μ (FIG. 5A); $\lambda_{MAX}^{ETOH} 224 m\mu$ (ϵ 16,000), $234 m\mu$ (ϵ 16,000), $277 m\mu$ (ϵ 6000) AND $326 m\mu$ (ϵ 3600). THE N.M.R. SPECTRUM OF 55 IS SHOWN IN FIG. 12B AND DISCUSSED ON PAGE 63.

ANAL. CALCD. FOR $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47.

FOUND: C, 65.11; H, 4.82; N, 3.80, 3.92.

PROCEDURE B A SOLUTION OF 0.500 G. OF 6-OXOCRINAMINE, 5 ML. DIMETHYL SULFOXIDE (DISTILLED) AND 3.5 ML. ACETIC ANHYDRIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 24 HOURS. THE MIXTURE WAS DILUTED WITH 300 ML. OF WATER AND EXTRACTED

THREE TIMES WITH BENZENE. THE BENZENE SOLUTION WAS WASHED TWICE WITH WATER, FILTERED THROUGH COTTON AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE (0.479 g.) WAS PURE BY THIN LAYER CHROMATOGRAPHY AND WAS RECRYSTALLIZED FROM ETHER-ACETONE. THE PRODUCT WAS IDENTICAL IN ALL RESPECTS TO THE PRODUCT OBTAINED IN PROCEDURE A.

6-HYDROXYCRINAMINE-6,11-D₂ (56)

A SOLUTION OF 0.314 g. 6,11-DIOXOCRINAMINE IN 20 ML. FRESHLY DISTILLED TETRAHYDROFURAN WAS STIRRED FOR TWO HOURS AT ICE TEMPERATURE IN THE PRESENCE OF 0.150 g. LITHIUM ALUMINUM DEUTERIDE (METAL HYDRIDES, 98.5%). THE EXCESS REDUCING AGENT WAS DESTROYED WITH A FEW DROPS OF WATER AND THE INORGANIC SALTS WERE REMOVED BY FILTRATION. THE ORGANIC SOLUTION WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.156 g. OF RESIDUE. A THIN LAYER CHROMATOGRAPH SHOWED THE PRESENCE OF TWO COMPONENTS, ONE OF WHICH HAD THE SAME RF VALUE AS 6-HYDROXYCRINAMINE. THE MIXTURE WAS CHROMATOGRAPHED ON 10 g. OF FLORISIL AND GAVE IN 3% METHANOL IN CHLOROFORM, 6-HYDROXYCRINAMINE-6,11-D₂ (0.091 g.). THE DEUTERATED DERIVATIVE WAS RECRYSTALLIZED FROM CHLOROFORM-ACETONE: M.P. 207-208°. THE INFRARED SPECTRUM OF 56 IS SHOWN IN FIG. 5B, AND THE N.M.R. SPECTRUM IS SHOWN IN FIG. 13B AND DISCUSSED ON PAGE 66.

ANAL. CALCD. FOR C₁₇H₁₇NO₅D₂: D, 2.00. FOUND: 1.59.

6-ACETYL-11-OXOCRINAMINE (57)

A SOLUTION OF 0.300 G. OF 6-HYDROXYCRINAMINE, 3 ML. OF DIMETHYLSULFOXIDE AND 2 ML. OF ACETIC ANHYDRIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 20 HOURS. THE REACTION MIXTURE WAS DILUTED WITH ABOUT 300 ML. OF WATER AND MADE SLIGHTLY BASIC (PH 9) WITH AQUEOUS AMMONIA. THE AQUEOUS SOLUTION WAS EXTRACTED THREE TIMES WITH BENZENE AND THE BENZENE SOLUTION WAS WASHED THREE TIMES WITH WATER. THE BENZENE SOLUTION WAS FILTERED THROUGH COTTON AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE (0.310 G.) WAS DISTILLED (0.001 MM., 150°) TO GIVE A GLASS: $[\alpha]_{589}^{25} +120^{\circ}$, $[\alpha]_{436}^{25} +410^{\circ}$; $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.70 μ AND 5.74 μ (FIG. 5c); $\lambda_{\text{MAX}}^{\text{ETOH}}$ 251 $m\mu$ (ϵ 4700), AND 293 $m\mu$ (ϵ 5100) WITH SHOULDERS AT 311 $m\mu$ (ϵ 3100) AND 323 $m\mu$ (ϵ 2100).
ANAL. CALCD. FOR $C_{19}H_{19}NO_6$: C, 63.86; H, 5.51; N, 3.92.
 FOUND: C, 63.44; H, 5.51; N, 3.94.

6-HYDROXY-11-OXOCRINAMINE (58)

6-ACETYL-11-OXOCRINAMINE (0.385 G.) WAS DISSOLVED IN A SOLUTION OF 0.030 M SODIUM METHOXIDE IN METHANOL (50 ML.) AND THE LIGHT YELLOW SOLUTION WAS KEPT AT 20° FOR 28 HOURS. A FEW DROPS OF GLACIAL ACETIC ACID WERE ADDED TO THE SOLUTION AND THE SOLUTION WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN 0.01 N HYDROCHLORIC ACID, MADE BASIC (PH 9) WITH AQUEOUS AMMONIA AND EXTRACTED WITH CHLOROFORM. THE ORGANIC SOLUTION WAS REDUCED TO DRYNESS TO GIVE 0.295 G. OF 6-HYDROXY-11-OXOCRINAMINE; $\lambda_{\text{MAX}}^{\text{CHCL}_3}$ 5.68 μ (FIG. 6A);

$\lambda_{\text{MAX}}^{\text{ETOH}}$ 246 μ , 293 μ AND 312 μ . THE N.M.R. SPECTRUM OF 58 IS SHOWN IN FIG. 15B AND DISCUSSED ON PAGE 73. THE BASE FORMED A PICRATE DERIVATIVE: M.P. 112-113⁰ (FROM METHANOL).

ANAL. CALCD. FOR $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_{12} \cdot 2\text{CH}_3\text{OH}$: C, 49.32; H, 4.60; N, 9.21. FOUND: C, 49.00; H, 4.51; N, 9.34.

THE RATE OF OXIDATION OF THE 6-HYDROXYCRINAMINE EPIMERS

A SOLUTION OF 0.600 G. OF 6-HYDROXYCRINAMINE IN 50 ML. OF CHLOROFORM WAS STIRRED AT ROOM TEMPERATURE WITH 2.00 G. OF ACTIVATED MANGANESE DIOXIDE.⁶⁵ AT GIVEN INTERVALS, ALIQUOTS OF THE MIXTURE WERE TAKEN, THE MANGANESE DIOXIDE REMOVED BY FILTRATION AND AN N.M.R. SPECTRUM OBTAINED. THE RELATIVE AREAS OF THE PEAKS AT 5.00 AND 5.35 P.P.M. ARE GIVEN IN TABLE 5.

TABLE 5. MANGANESE DIOXIDE OXIDATION OF 6-HYDROXYCRINAMINE

TIME ELAPSED	AREA OF PEAK AT		RATIO
	5.00 P.P.M.	5.35 P.P.M.	
0 MIN.	35	15	0.43
30 MIN.	19	9.2	0.48
60 MIN.	5	2.3	0.48

N-NITROSO-6-HYDROXYCRINAMINE (60)

TO A SOLUTION OF 0.300 G. OF 6-HYDROXYCRINAMINE IN 100 ML. OF 1.5% AQUEOUS ACETIC ACID WAS ADDED 0.300 G. OF SODIUM NITRITE. THE REACTION MIXTURE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 4 HOURS. AT THIS TIME A NEGATIVE ALKALOID TEST

WITH SILICOTUNGSTIC ACID WAS OBTAINED. THE AQUEOUS SOLUTION WAS EXTRACTED THREE TIMES WITH CHLOROFORM, AND THE CHLOROFORM SOLUTION WAS WASHED WITH 5% SODIUM BICARBONATE SOLUTION. EVAPORATION OF THE CHLOROFORM SOLUTION UNDER REDUCED PRESSURE GAVE 0.310 G. OF CRYSTALLINE RESIDUE WHICH WAS RECRYSTALLIZED FROM ETHANOL-ACETONE: M.P. 207-208°; $[\alpha]_{589}^{25} +345^{\circ}$, $[\alpha]_{436}^{25} +875^{\circ}$ (c 0.24); $\lambda_{\text{MAX}}^{\text{NUJOL}} 2.69 \mu$ (FIG. 17A); $\lambda_{\text{MAX}}^{\text{ETOH}} 239 \text{ m}\mu$ ($\epsilon 14,000$) AND 290 $\text{m}\mu$ ($\epsilon 4800$). THE N.M.R. SPECTRUM OF 60 IS PRESENTED IN FIG. 18A AND DISCUSSED ON PAGE 82.

ANAL. CALCD. FOR $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6$: C, 58.95; H, 5.24; N, 8.09.
 FOUND: C, 59.31; H, 5.41; N, 8.00.

N-NITROSOLACTONE (61)

A SOLUTION OF 0.310 G. OF N-NITROSO-6-HYDROXYCRINAMINE IN 80 ML. OF CHLOROFORM WAS STIRRED FOR 6 HOURS WITH 1.50 G. OF MANGANESE DIOXIDE AT ROOM TEMPERATURE. THE MANGANESE DIOXIDE WAS REMOVED BY FILTRATION, AND THE SOLVENT WAS CONCENTRATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.285 G. OF RESIDUE WHICH CRYSTALLIZED UPON TRITURATION WITH ETHER. RECRYSTALLIZATION FROM ACETONE-METHANOL-CHLOROFORM GAVE WHITE PRISMS: M.P. 251-252°; $[\alpha]_{589}^{25} +360^{\circ}$, $[\alpha]_{436}^{25} +880^{\circ}$ (c 0.15, PYRIDINE) $\lambda_{\text{MAX}}^{\text{KBR}} 5.80 \mu$ AND 6.19 μ (FIG. 17B); $\lambda_{\text{MAX}}^{\text{ETOH}} 231 \text{ m}\mu$ ($\epsilon 35,000$), 266 $\text{m}\mu$ ($\epsilon 6800$) AND 308 $\text{m}\mu$ ($\epsilon 7200$).

ANAL. CALCD. FOR $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_6$: C, 59.30; H, 4.68; N, 8.14.
 FOUND: C, 59.12; H, 4.66; N, 7.91.

ACETYLATION OF DIHYDRO-6-HYDROXYCRINAMINE AT 110°

TO A SOLUTION OF 0.390 G. OF DIHYDRO-6-HYDROXYCRINAMINE IN 10 ML. OF REFLUXING PYRIDINE, 2 ML. OF ACETIC ANHYDRIDE WAS ADDED DROPWISE OVER A 10 MINUTE PERIOD. THE TEMPERATURE WAS MAINTAINED AT 110° FOR ANOTHER 20 MINUTES. THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE TO GIVE 0.410 G. OF RESIDUE. THE RESIDUE WAS DISTILLED TO A GLASS: $\lambda_{\text{MAX}}^{\text{KBR}} 5.74 \mu$ (FIG. 17C); THE N.M.R. SPECTRUM IS PRESENTED IN FIG. 18B AND DISCUSSED ON PAGE 86.

6-HYDROXYCRINAMINE-6-D

A SOLUTION OF 0.200 G. OF 6-OXOCRINAMINE IN 20 ML. OF DRY TETRAHYDROFURAN WAS TREATED WITH 0.100 G. OF LITHIUM ALUMINUM DEUTERIDE FOR 2 HOURS AT 0°. THE EXCESS REDUCING AGENT WAS DESTROYED WITH WATER AND THE INORGANIC SALTS REMOVED BY FILTRATION. THE FILTRATE WAS CONCENTRATED TO DRYNESS UNDER REDUCED PRESSURE TO PROVIDE 0.205 G. OF AMORPHOUS MATERIAL WHICH CRYSTALLIZED UPON SEEDING WITH 6-HYDROXYCRINAMINE. THE 6-HYDROXYCRINAMINE-6-D WAS RECRYSTALLIZED FROM CHLOROFORM-ACETONE: M.P. 209-210°; $[\alpha]_{589}^{25} +62^\circ$, $[\alpha]_{436}^{25} +167^\circ$ (c 0.45). THE DEUTERIUM INCORPORATION WAS GREATER THAN 95% AS DETERMINED BY N.M.R. SPECTROSCOPY.

N-METHYL-11-ACETYL-6-HYDROXYCRINAMINE (72)

A SOLUTION OF 0.300 G. OF 11-ACETYL-6-HYDROXYCRINAMINE, 2 ML. OF METHYL IODIDE AND 10 ML. OF ACETONE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 2 HOURS. THE SOLVENTS WERE

REMOVED UNDER REDUCED PRESSURE AND THE RESIDUE WAS DISSOLVED IN WATER. THE AQUEOUS SOLUTION WAS MADE BASIC (PH 9) WITH AQUEOUS AMMONIA AND ALLOWED TO STAND AT ROOM TEMPERATURE FOR 10 MINUTES. EXTRACTION WITH CHLOROFORM AND EVAPORATION OF THIS SOLVENT YIELDED 0.280 G. OF A LIGHT BROWN RESIDUE. THE RESIDUE RESISTED ALL ATTEMPTS OF CRYSTALLIZATION, NOR WOULD IT MIGRATE ON T.L.C. PLATES (SILICA GEL G) WITH SOLVENTS AND MIXTURES OF SOLVENTS RANGING IN POLARITY FROM BENZENE TO 95% ETHANOL. ALTHOUGH THE COMPOUND WAS READILY SOLUBLE IN CHLOROFORM, ELUTION FROM NEUTRAL ALUMINA OR FLORISIL ALSO WAS UNSUCCESSFUL. THE ALDEHYDE CARBONYL APPEARED IN THE INFRARED SPECTRUM AT 5.99μ (SEE FIG. 19A). THE N.M.R. SPECTRUM OF 72 IS SHOWN IN FIG. 20A AND DISCUSSED ON PAGE 95. 11-ACETYL-N-METHYL-6-HYDROXYCRINAMINE ABSORBED IN THE ULTRAVIOLET AT 315 AND 288 $m\mu$ ($CHCl_3$) AND AT 290 $m\mu$ AND 241 $m\mu$ (95% ETHANOL).

HYDROXYLAMINE ADDUCT (73)

PROCEDURE A TO A SOLUTION OF 0.070 G. OF 72 IN 20 ML. OF 95% ETHANOL WAS ADDED 1.00 G. OF SODIUM ACETATE AND 0.100 G. OF HYDROXYLAMINE HYDROCHLORIDE. THE BUFFERED SOLUTION WAS REFLUXED FOR THREE HOURS. THE SOLVENT WAS REMOVED UNDER REDUCED PRESSURE AND THE RESIDUE WAS DISSOLVED IN WATER. THE SUSPENSION WAS MADE BASIC (PH 9) WITH AQUEOUS AMMONIA AND EXTRACTED TWICE WITH CHLOROFORM. THE CHLOROFORM WAS REDUCED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.058 G. OF PRODUCT. THE RESIDUE CRYSTALLIZED UPON TRITURATION WITH ETHYL ACETATE AND WAS

RECRYSTALLIZED FROM ETHYL ACETATE AS PRISMS: M.P. 204-205°; $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.75 μ (FIG. 19B); $\lambda_{\text{MAX}}^{\text{ETOH}}$ 236 $m\mu$ (ϵ 2100) AND 293 $m\mu$ (ϵ 3500). THE N.M.R. SPECTRUM OF 73 IS SHOWN IN FIG. 20B AND DISCUSSED ON PAGE 98.

ANAL. CALCD. FOR $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_6$: C, 61.84; H, 6.23; N, 7.21.
 FOUND: C, 61.69; H, 6.28; N, 6.99.

PROCEDURE B A SOLUTION OF 0.240 G. OF 72 IN 10 ML. OF ANHYDROUS PYRIDINE AND 10 ML. OF ABSOLUTE ETHANOL WAS REFLUXED FOR THREE HOURS WITH 0.300 G. OF HYDROXYLAMINE HYDROCHLORIDE. THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE AND THE RESIDUE DISSOLVED IN WATER. THE AQUEOUS SOLUTION WAS MADE BASIC WITH AQUEOUS AMMONIA AND EXTRACTED THREE TIMES WITH CHLOROFORM. THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.220 G. OF RESIDUE. THE RESIDUE WAS TRITURATED WITH ETHYL ACETATE AND RECRYSTALLIZED FROM ETHYL ACETATE. THE DERIVATIVE WAS FOUND TO BE IDENTICAL IN ALL RESPECTS TO THAT COMPOUND OBTAINED IN PROCEDURE A.

N-ACETYL HYDROXYLAMINE ADDUCT (74)

A SOLUTION OF 0.150 G. OF 73 IN 5 ML. OF PYRIDINE AND 2 ML. OF ACETIC ANHYDRIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 24 HOURS. THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE AND THE RESIDUE WAS CHROMATOGRAPHED OVER FLORISIL (10 G.). THE ACETYLATED DERIVATIVE WAS ELUTED IN 100% ETHYL ACETATE AND WAS PURE BY T.L.C. THE COMPOUND WAS SUBLIMED (135°, 0.01 MM.) TO A GLASS: $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.75 AND 5.98 μ (FIG. 19C);

$\lambda_{\text{MAX}}^{\text{ETOH}}$ 234 $\text{m}\mu$ (ϵ 5700) AND 292 $\text{m}\mu$ (ϵ 5600). THE N.M.R. SPECTRUM OF 74 IS SHOWN IN FIG. 21A AND DISCUSSED ON PAGE 99.

ANAL. CALCD. FOR $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_7$: C, 61.38; H, 6.09; N, 6.51.

FOUND: C, 60.63; H, 6.18; N, 6.31.

6A-EPI-N-DEMETHYLMACRONINE (82)

A SOLUTION OF 0.500 G. OF 6-OXOCRINAMINE IN 10 ML. OF ANHYDROUS PYRIDINE WAS TREATED WITH 1.0 ML. OF METHANESULFONYL CHLORIDE AND THE SOLUTION WAS ALLOWED TO STAND AT 4° FOR 24 HOURS. AN AQUEOUS SOLUTION OF 7.0 G. OF SODIUM BICARBONATE WAS ADDED SLOWLY TO THE PYRIDINE SOLUTION WHICH WAS COOLED IN AN ICE BATH. THE AQUEOUS SOLUTION WAS ALLOWED TO STAND AT ICE TEMPERATURE FOR 24 HOURS AND THEN EXTRACTED THREE TIMES WITH CHLOROFORM. THE CHLOROFORM SOLUTION WAS FILTERED THROUGH COTTON AND EVAPORATED TO DRYNESS TO GIVE 0.380 G. OF RESIDUE. THE RESIDUE WAS CHROMATOGRAPHED OVER 30 G. OF FLORISIL TO GIVE IN 100% CHLOROFORM 0.210 G. OF 82. THE LACTONE WAS RECRYSTALLIZED FROM ETHYL ACETATE TO GIVE PRISMS: M.P. $160-161^\circ$;

$[\alpha]_{589}^{25} +130^\circ$, $[\alpha]_{436}^{25} +310^\circ$; $\lambda_{\text{MAX}}^{\text{KBR}}$ 5.80 μ AND 6.17 μ (FIG. 6B); $\lambda_{\text{MAX}}^{\text{ETOH}}$ 230 $\text{m}\mu$ (ϵ 24,000), 267 $\text{m}\mu$ (ϵ 6100) AND 308 $\text{m}\mu$ (ϵ 6000).

THE N.M.R. SPECTRUM OF 82 IS SHOWN IN FIG. 21B AND DISCUSSED ON PAGE 105.

ANAL. CALCD. FOR $\text{C}_{17}\text{H}_{17}\text{NO}_5$: C, 64.75; H, 5.43; N, 4.44.

FOUND: C, 64.83; H, 5.41; N, 4.52.

CRIWELLINE-8-D₂ (94)

A SOLUTION OF 0.040 G. OF 6-HYDROXYCRINAMINE-6,11-D₂ IN ACETONE (10 ML.) WAS TREATED WITH 1 ML. OF METHYL IODIDE. THE SOLUTION WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR ONE HOUR AT WHICH TIME THE SOLVENT WAS REMOVED UNDER REDUCED PRESSURE. THE RESULTING METHIODIDE WAS DISSOLVED IN WATER AND THE AQUEOUS SOLUTION WAS MADE BASIC (PH > 12) WITH 20% SODIUM HYDROXIDE. THE AQUEOUS SOLUTION WAS EXTRACTED THREE TIMES WITH CHLOROFORM AND THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.042 G. OF 94. THE DEUTERATED DERIVATIVE WAS RECRYSTALLIZED FROM ACETONE-CHLOROFORM TO GIVE PRISMS: M.P. 206-207°. THE INFRARED SPECTRUM IS PRESENTED IN FIG. 6C AND THE N.M.R. SPECTRUM OF 94 IS SHOWN IN FIG. 25A AND DISCUSSED ON PAGE 119.

ANAL. CALCD. FOR C₁₈H₁₉NO₅D₂: D, 2.00. FOUND: D, 1.59

6-HYDROXYCRINAMINE AND HYDROXYLAMINE

TO A SOLUTION OF 0.380 G. OF 6-HYDROXYCRINAMINE IN 25 ML. OF 95% ETHANOL WAS ADDED A SOLUTION OF 1.47 G. OF SODIUM ACETATE AND 0.768 G. OF HYDROXYLAMINE HYDROCHLORIDE IN 9 ML. OF WATER. THE SOLUTION WAS REFLUXED FOR 24 HOURS AND THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN WATER, MADE BASIC (PH 9) WITH AQUEOUS AMMONIA AND EXTRACTED THREE TIMES WITH CHLOROFORM. THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.350 G. OF RESIDUE. THE INFRARED SPECTRUM OF THE RESIDUE WAS IDENTICAL WITH THAT

OF 6-HYDROXYCRINAMINE. THE ALKALOID WAS RECRYSTALLIZED FROM ACETONE-CHLOROFORM TO GIVE NEEDLES: M.P. 211-212^o, MIXTURE M.P. WITH 6-HYDROXYCRINAMINE, 210-212^o.

DIHYDROCRIWELLINE (99)

A SOLUTION OF 0.100 G. OF CRIWELLINE IN GLACIAL ACETIC ACID WAS ADDED TO A PREEQUILIBRATED SUSPENSION OF PLATINUM (0.074 G.) IN THE SAME SOLVENT UNDER HYDROGEN. FOUR HOURS LATER THE ABSORPTION OF HYDROGEN STOPPED AFTER 8.4 ML. OF HYDROGEN (110%) HAD BEEN TAKEN UP. THE SOLUTION WAS FILTERED AND CONCENTRATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN WATER, MADE BASIC WITH AQUEOUS AMMONIA AND EXTRACTED WITH CHLOROFORM. THE SOLVENT WAS REMOVED UNDER REDUCED PRESSURE TO GIVE A COLORLESS GUM (0.082 G.). THE GUM WAS DISTILLED TO A GLASS BUT WOULD NOT CRYSTALLIZE. THE N.M.R. SPECTRUM IS SHOWN IN FIG. 21A AND DISCUSSED ON PAGE 129. DIHYDROCRIWELLINE FORMED A PICRATE DERIVATIVE WHICH WAS RECRYSTALLIZED FROM METHANOL TO GIVE NEEDLES: M.P. 225-227^o.

ANAL. CALCD. FOR $C_{24}H_{26}N_4O_{12}$: C, 51.24; H, 4.67; N, 9.96.

FOUND: C, 51.30; H, 4.80; N, 10.00.

CRIWELLINEDIOL (101)

A SOLUTION OF 0.850 G. OF CRIWELLINE AND 0.420 G. OF LITHIUM ALUMINUM HYDRIDE IN 45 ML. OF FRESHLY DISTILLED TETRAHYDROFURAN WAS REFLUXED FOR THREE HOURS. UPON COOLING, THE EXCESS LITHIUM ALUMINUM HYDRIDE WAS DESTROYED BY SLOWLY ADDING

DROPS OF WATER. THE SUSPENSION WAS FILTERED THROUGH CELITE AND THE SOLVENT WAS REMOVED UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN CHLOROFORM AND THE ORGANIC SOLUTION WAS WASHED TWICE WITH WATER. THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.710 G. OF CLEAR RESIDUE WHICH FORMED CRYSTALS UPON TRITURATION WITH ACETONE. THE DIOL WAS RECRYSTALLIZED FROM ACETONE TO GIVE NEEDLES: M.P. 99-100°; $[\alpha]_{589}^{25} +62^{\circ}$, $[\alpha]_{436}^{25} +152^{\circ}$ (c 0.44); $\lambda_{\text{MAX}}^{\text{KBR}}$ 2.68, 3.06, 3.43, 3.55, 6.45, 9.30 AND 10.62 μ ; $\lambda_{\text{MAX}}^{\text{ETOH}}$ 241 $m\mu$ (ϵ 6800) AND 287 $m\mu$ (ϵ 4900). THE N.M.R. SPECTRUM OF CRIWELLINEDIOL IS PRESENTED IN FIG. 28A AND DISCUSSED ON PAGE 132.

ANAL. CALCD. FOR $\text{C}_{18}\text{H}_{23}\text{NO}_5$: C, 64.85; H, 6.95; N, 4.20.
 FOUND: C, 64.64; H, 7.24; N, 3.85.

CRIWELLINE-N-D₃

A SOLUTION OF 0.200 G. OF 6-HYDROXYCRINAMINE AND 1.5 ML. OF METHYL IODIDE-D₃⁶⁶ IN 10 ML. OF METHANOL-ACETONE (1:5) WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 30 MINUTES. THE EXCESS METHYL IODIDE-D₃ AND SOLVENTS WERE REMOVED BY DISTILLATION AND COLLECTED IN A LIQUID NITROGEN TRAP. THE RESIDUE WAS DRIED AT ROOM TEMPERATURE UNDER REDUCED PRESSURE, DISSOLVED IN WATER AND MADE BASIC (PH 10) WITH 10% SODIUM HYDROXIDE. THE BASIC SOLUTION WAS EXTRACTED THREE TIMES WITH CHLOROFORM AND THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.202 G. OF CRIWELLINE-N-D₃, M.P. 201-202° FROM ACETONE-CHLOROFORM. THE DEUTERIUM INCORPORATION WAS GREATER THAN 98% AS

DETERMINED BY MASS SPECTROMETRY (FIG. 30B) AND BY THE COMPLETE ABSENCE OF THE N-METHYL PEAK IN THE N.M.R. SPECTRUM OF CRIWELLINE-N-D₃.

TAZETTINE-N-D₃

THE METHYL IODIDE-D₃ SOLUTION RECOVERED IN THE PREPARATION OF CRIWELLINE-N-D₃ WAS ADDED TO 0.050 G. OF HAEMANTHIDINE. THE SOLUTION WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 30 MINUTES. THE SOLVENTS WERE REMOVED BY DISTILLATION AND COLLECTED IN A LIQUID NITROGEN TRAP. THE RESIDUE WAS DRIED UNDER REDUCED PRESSURE, DISSOLVED IN WATER, AND MADE BASIC (PH 10) WITH 10% SODIUM HYDROXIDE. THE AQUEOUS SOLUTION WAS EXTRACTED THREE TIMES WITH CHLOROFORM AND THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.042 G. OF TAZETTINE-N-D₃ WHICH WAS RECRYSTALLIZED TWICE FROM ACETONE AND SUBLIMED AT 200° (0.001 MM), M.P. 211-213°. THE MASS SPECTRUM OF TAZETTINE-N-D₃ (FIG. 31B) INDICATED THAT THE DEUTERIUM INCORPORATION WAS GREATER THAN 98%.

N-DEMETHYLMACRONINE (115)

A SOLUTION OF 0.160 G. OF 6-OXOCRINAMINE IN 3 ML. OF 95% ETHANOL WAS ADDED TO A SOLUTION OF 0.45 ML. OF GLACIAL ACETIC ACID AND 1.150 G. OF SODIUM ACETATE IN 9 ML. OF WATER AND THE MIXTURE WAS REFLUXED FOR 3 HOURS. THE COOLED SOLUTION WAS DILUTED WITH WATER, MADE BASIC WITH AQUEOUS AMMONIA AND EXTRACTED WITH CHLOROFORM. THE CHLOROFORM SOLUTION WAS DRIED OVER

ANHYDROUS SODIUM SULFATE AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.140 G. OF PRODUCT. THE RESIDUE FORMED CRYSTALS UPON TRITURATION WITH ETHYL ACETATE AND WAS RECRYSTALLIZED FROM ETHYL ACETATE AS NEEDLES: M.P. 172-174°; $[\alpha]_{589}^{25} +300^\circ$, $[\alpha]_{436}^{25} +650^\circ$; $\lambda_{\text{MAX}}^{\text{KBR}} 5.80 \mu$ AND 6.18μ (FIG. 32A); $\lambda_{\text{MAX}}^{\text{ETOH}} 228 \text{ m}\mu$ ($\epsilon 27,000$), $268 \text{ m}\mu$ ($\epsilon 4700$) AND $305 \text{ m}\mu$ ($\epsilon 5500$). THE N.M.R. SPECTRUM OF 115 IS PRESENTED IN FIG. 33A AND DISCUSSED ON PAGE 148.

ANAL. CALCD. FOR $\text{C}_{17}\text{H}_{17}\text{NO}_5$: C, 64.75; H, 5.43; N, 4.44.
 FOUND: C, 64.54; H, 5.68; N, 4.16.

MACRONINE FROM N-DEMETHYLMACRONINE

A SOLUTION OF 0.200 G. OF N-DEMETHYLMACRONINE IN 10 ML. OF METHANOL CONTAINING 0.100 G. OF BORIC ACID AND ONE ML. OF 36% FORMALDEHYDE WAS TREATED WITH 0.200 G. OF SODIUM BOROHYDRIDE AND ALLOWED TO STAND AT ROOM TEMPERATURE FOR 15 MINUTES. THE SOLUTION WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE AND THE RESIDUE WAS DISSOLVED IN CHLOROFORM. THE CHLOROFORM SOLUTION WAS WASHED WITH WATER, DRIED OVER ANHYDROUS POTASSIUM CARBONATE AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.180 G. OF RESIDUE. THE RESIDUE WAS CHROMATOGRAPHED OVER 18 G. OF FLORISIL TO GIVE IN ETHYL ACETATE : BENZENE (1:1), 0.140 G. OF MACRONINE. THE ALKALOID WAS RECRYSTALLIZED FROM ACETONE-HEXANE AS NEEDLES: M.P. 199-200°; $[\alpha]_{589}^{25} +310^\circ$, $[\alpha]_{436}^{25} +690^\circ$; $\lambda_{\text{MAX}}^{\text{KBR}} 5.80 \mu$ AND 6.17μ (FIG. 32B); $\lambda_{\text{MAX}}^{\text{ETOH}} 227 \text{ m}\mu$ ($\epsilon 27,000$), $267 \text{ m}\mu$ ($\epsilon 5400$) AND $306 \text{ m}\mu$ ($\epsilon 6200$). THE N.M.R.

SPECTRUM OF MACRONINE IS PRESENTED IN FIG. 33B AND DISCUSSED ON PAGE 137.

ANAL. CALCD. FOR $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25.

FOUND: C, 65.57; H, 5.91; N, 4.10.

6A-DEOXY-8-METHOXYCRIWELLINE (117)

A SOLUTION OF 0.300 G. OF 6-HYDROXYCRINAMINE AND 3 ML. OF METHYL IODIDE IN 20 ML. OF METHANOL WAS REFLUXED FOR 12 HOURS. THE SOLVENT WAS REMOVED UNDER REDUCED PRESSURE AND THE RESULTING METHIODIDE DISSOLVED IN WATER. THE AQUEOUS SOLUTION WAS MADE BASIC (PH 9) WITH AQUEOUS AMMONIA AND EXTRACTED WITH CHLOROFORM. THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE TO GIVE A RESIDUE WHICH BY T.L.C. CONTAINED A SMALL AMOUNT OF CRIWELLINE AND MAINLY 117. THE MIXTURE WAS CHROMATOGRAPHED OVER FLORISIL TO GIVE IN 100% ETHYL ACETATE, 0.210 G. OF 117. THE DERIVATIVE WAS RECRYSTALLIZED FROM ETHER-HEXANE AS NEEDLES: M.P. 118-120°; $[\alpha]_{589}^{25} +240^{\circ}$, $[\alpha]_{436}^{25} +560^{\circ}$; λ_{MAX}^{ETOH} 241 m μ (ϵ 6300) AND 290 m μ (ϵ 4100). THE INFRARED SPECTRUM OF 117 IS SHOWN IN FIG. 32C AND THE N.M.R. SPECTRUM IS PRESENTED IN FIG. 29B AND DISCUSSED ON PAGE 155.

ANAL. CALCD. FOR $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06.

FOUND: C, 66.44; H, 6.65; N, 4.11.

MACRONINE FROM 6A-DEOXY-8-METHOXYCRIWELLINE

A SOLUTION OF 0.125 G. OF 117 IN 10 ML. OF GLACIAL ACETIC ACID WAS ADDED TO A STIRRING SOLUTION OF 0.100 G. OF CHROMIUM TRIOXIDE IN 8 ML. OF GLACIAL ACETIC ACID OVER A TWO HOUR

PERIOD. THE SOLUTION WAS STIRRED FOR ONE ADDITIONAL HOUR AND THE DARK GREEN SOLUTION WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE GUMMY RESIDUE WAS DISSOLVED IN 1 N HYDROCHLORIC ACID AND THE SOLUTION WAS WASHED WITH CHLOROFORM AND MADE BASIC (PH 9) WITH AQUEOUS AMMONIA. THE BASIC SOLUTION WAS EXTRACTED WITH CHLOROFORM AND THE CHLOROFORM REMOVED UNDER REDUCED PRESSURE TO GIVE 0.065 G. OF A RESIDUE. THE RESIDUE WAS CHROMATOGRAPHED OVER 10 G. OF BASIC ALUMINA (MERCK). MACRONINE (0.024 G.) WAS ELUTED IN 100% ETHYL ACETATE AND RECRYSTALLIZED FROM ACETONE-HEXANE AS NEEDLES, M.P. 199-201^o. AN INFRARED OF THIS COMPOUND WAS IDENTICAL TO THAT OF THE MACRONINE OBTAINED ABOVE AND TO THAT OF AUTHENTIC MACRONINE, OBTAINED THROUGH THE GENEROSITY OF D. STAUFFACHER.

6-HYDROXYCRINAMINE-11-D

A SOLUTION OF 0.280 G. OF 6-ACETYL-11-OXOCRINAMINE IN 25 ML. OF FRESHLY DISTILLED TETRAHYDROFURAN WAS STIRRED AND COOLED IN AN ICE BATH WHILE 0.010 G. OF LITHIUM ALUMINUM DEUTERIDE WAS ADDED. THE SOLUTION WAS STIRRED FOR TWO HOURS AT ICE TEMPERATURE AND ONE HOUR AT ROOM TEMPERATURE. THE SOLUTION WAS COOLED AGAIN IN AN ICE BATH AND 0.100 G. OF LITHIUM ALUMINUM HYDRIDE WAS ADDED TO INSURE REDUCTION. AFTER ONE ADDITIONAL HOUR THE EXCESS REDUCING AGENT WAS DESTROYED BY ADDING A FEW DROPS OF WATER. THE INORGANIC SALTS WERE REMOVED BY FILTRATION THROUGH CELITE AND THE SOLVENT REMOVED UNDER REDUCED PRESSURE. THE RESIDUE (0.210 G.) WAS CHROMATOGRAPHED ON 20 G. OF

FLORISIL. 6-HYDROXYCRINAMINE-11-D (0.090 g.) WAS ELUTED IN 3-5% METHANOL IN CHLOROFORM AND RECRYSTALLIZED FROM ACETONE-CHLOROFORM AS NEEDLES, M.P. 210-212⁰. THE MASS SPECTRUM SHOWED A PARENT ION RELATIVE INTENSITY OF 33.0 AND THE P+1 PEAK HAD A RELATIVE INTENSITY OF 23.1.

6-HYDROXYCRINAMINE-11-H³

A SOLUTION OF 0.380 g. OF 6-ACETYL-11-OXOCRINAMINE IN 25 ML. OF FRESHLY DISTILLED TETRAHYDROFURAN WAS STIRRED AND COOLED IN AN ICE BATH WHILE 0.012 g. OF LITHIUM ALUMINUM HYDRIDE-H³ (25.0 MILLICURIES) WAS ADDED. THE SOLUTION WAS STIRRED FOR ONE HOUR IN THE ICE BATH AND FOR THREE ADDITIONAL HOURS AT 25⁰. THE SOLUTION WAS COOLED IN AN ICE BATH AND 0.200 g. OF LITHIUM ALUMINUM HYDRIDE WAS ADDED TO INSURE REDUCTION. THE SOLUTION WAS STIRRED AN ADDITIONAL 90 MINUTES. THE EXCESS REDUCING AGENT WAS DESTROYED WITH A FEW DROPS OF WATER AND THE INORGANIC SALTS WERE REMOVED BY FILTRATION. THE FILTRATE WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE TO GIVE 0.218 g. OF RESIDUE. THE RESIDUE WAS CHROMATOGRAPHED ON 20 g. OF FLORISIL AND 0.102 g. OF 6-HYDROXYCRINAMINE-11-H³ WAS ELUTED WITH 3% METHANOL IN CHLOROFORM. THE RADIOACTIVE ALKALOID WAS RECRYSTALLIZED TWICE FROM CHLOROFORM-ACETONE TO GIVE 0.068 g. OF PURE 6-HYDROXYCRINAMINE-11-H³; M.P. 209-211⁰; 1.24×10^8 DPM/MG. = 3.6 MILLICURIES/65 MG. = 3.92 DPM/MMOLE.*

*A PACKARD TRI-CARB LIQUID SCINTILLATION SPECTROMETER SYSTEM WAS USED TO DETERMINE THE RADIOACTIVITY OF ALL SAMPLES CITED.

6-ACETYL-11-OXOCRINAMINE FROM 6-HYDROXYCRINAMINE-11-H³

A SOLUTION OF 0.100 G. OF 6-HYDROXYCRINAMINE-11-H³ (3.92×10^6 DPM/MMOLE), 2 ML. OF DIMETHYLSULFOXIDE AND 1 ML. OF ACETIC ANHYDRIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 24 HOURS. THE SOLUTION WAS DILUTED WITH 200 ML. OF WATER AND 10 ML. OF 6 N AMMONIUM HYDROXIDE. THE SOLUTION WAS EXTRACTED THREE TIMES WITH BENZENE AND THE BENZENE WAS WASHED TWICE WITH WATER. THE BENZENE WAS REMOVED UNDER REDUCED PRESSURE TO GIVE 0.132 G. OF A CLEAR GUM. THE 6-ACETYL-11-OXOCRINAMINE WAS DISTILLED (150° , 0.01 MM), AND ITS RADIOACTIVITY DETERMINED AS 2.15 DPM/MMOLE.

CRIWELLINE-8-H³

A SOLUTION OF 0.210 G. OF 6-HYDROXYCRINAMINE-11-H³ (3.92×10^6 DPM/MMOLE) IN 20 ML. OF ACETONE CONTAINING 3 ML. OF METHYL IODIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 30 MINUTES. THE SOLVENT AND EXCESS METHYL IODIDE WAS REMOVED UNDER REDUCED PRESSURE TO GIVE THE METHIODIDE. THE METHIODIDE WAS DISSOLVED IN WATER AND THE AQUEOUS SOLUTION MADE BASIC (PH > 12) WITH 1 N SODIUM HYDROXIDE. THE BASIC SOLUTION WAS EXTRACTED THREE TIMES WITH CHLOROFORM AND THE CHLOROFORM WAS EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE (0.212 G.) CRYSTALLIZED UPON TRITURATION WITH ACETONE AND WAS RECRYSTALLIZED FROM ACETONE-CHLOROFORM AS PRISMS: M.P. 204-205^o; 2.99×10^6 DPM/MMOLE.

ACID AND BASE EQUILIBRATION OF 6-HYDROXYCRINAMINE-11-H³

6-HYDROXYCRINAMINE-11-H³ (0.100 g., 3.88×10^6 DPM/MMOLE) WAS DISSOLVED IN 1 N HYDROCHLORIC ACID AND SHAKEN IN A SEPARATORY FUNNEL. THE SOLUTION WAS MADE BASIC ($\text{PH} > 12$) WITH 5 N SODIUM HYDROXIDE AND ALLOWED TO STAND AT ROOM TEMPERATURE FOR 15 MINUTES. THE BASIC SOLUTION WAS EXTRACTED WITH CHLOROFORM AND THE CHLOROFORM EXTRACT WASHED WITH WATER. THE CHLOROFORM WAS REMOVED UNDER REDUCED PRESSURE AND GAVE 0.089 g. OF RESIDUE. THE 6-HYDROXYCRINAMINE-11-H³ WAS RECRYSTALLIZED FROM CHLOROFORM-ACETONE AS NEEDLES: M.P. 211-212⁰; 3.95×10^6 DPM/MMOLE.

ACID AND BASE EQUILIBRATION OF CRIWELLINE-8-H³

A SOLUTION OF 0.050 g. OF CRIWELLINE-8-H³ (2.99×10^6 DPM/MMOLE) IN 1 N HYDROCHLORIC ACID WAS SHAKEN IN A SEPARATORY FUNNEL AND MADE BASIC ($\text{PH} > 12$) WITH 5 N SODIUM HYDROXIDE. THE BASIC SOLUTION WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 15 MINUTES AND THEN IT WAS EXTRACTED WITH CHLOROFORM. THE CHLOROFORM SOLUTION WAS WASHED WITH WATER AND EVAPORATED TO DRYNESS UNDER REDUCED PRESSURE. THE RECOVERED CRIWELLINE (0.045 g.) WAS RECRYSTALLIZED FROM CHLOROFORM-ACETONE AS PRISMS: M.P. 203-205⁰; 2.92×10^6 DPM/MMOLE.

BASE EQUILIBRATION OF TAZETTADIOL

A SOLUTION OF 0.210 g. OF TAZETTADIOL IN 5 ML. OF DIOXANE WAS ADDED TO A SOLUTION OF 1 N SODIUM DEUTEROXIDE IN DEUTERIUM OXIDE AND THE MIXTURE WAS ALLOWED TO STAND AT ROOM TEMPERATURE

FOR 30 MINUTES. THE SOLUTION WAS EXTRACTED WITH CHLOROFORM AND THE CHLOROFORM SOLUTION WAS FILTERED THROUGH COTTON AND EVAPORATED TO DRYNESS. THE RESIDUE WAS PURE TAZETTADIOL BY T.L.C. AND AN N.M.R. SPECTRUM WAS OBTAINED. NO DEUTERIUM INCORPORATION WAS FOUND IN THE BENZYLIC PROTONS AS DETERMINED BY THE INTEGRAL OF THE SPECTRUM.

6-HYDROXYCRINAMINE-11-H³ METHIODIDE

A SOLUTION OF 6-HYDROXYCRINAMINE-11-H³ (4.70×10^6 DPM/MMOLE) IN 10 ML. OF METHANOL-ACETONE 1:5 AND 2 ML. OF METHYL IODIDE WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 10 MINUTES. THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE AND THE METHIODIDE WAS ISOLATED AND RECRYSTALLIZED AS THE MONOHYDRATE: M.P. 169-170° (LITERATURE VALUE, M.P. 174⁰²⁶); 4.54×10^6 DPM/MMOLE.

LOSS OF RADIOACTIVITY DURING THE 6-HYDROXYCRINAMINE-CRIWELLINE REARRANGEMENT

6-HYDROXYCRINAMINE-11-H³ METHIODIDE (0.248 g., 190×10^6 DPM) WAS DISSOLVED IN 30 ML. OF WATER AND 1 ML. OF 10 N SODIUM HYDROXIDE WAS ADDED TO EFFECT THE REARRANGEMENT. THE AQUEOUS SOLUTION WAS EXTRACTED 4 TIMES WITH CHLOROFORM AND A NEGATIVE ALKALOID TEST (SILICOTUNGSTIC ACID) WAS OBTAINED. THE RADIOACTIVITY OF THE AQUEOUS SOLUTION WAS OBTAINED BY COUNTING A 1 ML. ALIQUOT. THE TOTAL RADIOACTIVITY IN THE AQUEOUS SOLUTION WAS 1.6×10^5 DPM OR 8.5% OF THAT OF THE METHIODIDE.

HOFMANN DEGRADATION OF CRIWELLINE-8-H³

A SOLUTION OF 0.180 G. OF CRIWELLINE-8-H³ (1.00×10^6 DPM/MMOLE) AND 1 ML. OF METHYL IODIDE IN 10 ML. OF ACETONE WAS REFLUXED FOR 2 HOURS. THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE AND THE RESULTING METHIODIDE WAS DISSOLVED IN 5 ML. OF WATER AND ADDED TO A 0.50 G. SUSPENSION OF FRESHLY PREPARED SILVER OXIDE. THE MIXTURE WAS STIRRED IN THE DARK FOR 5 HOURS. THE INORGANIC SALTS WERE REMOVED BY FILTRATION THROUGH CELITE, AND THE FILTRATE WAS CONCENTRATED TO DRYNESS UNDER REDUCED PRESSURE. THE RESIDUE WAS HEATED ON THE STEAM BATH AN ADDITIONAL 30 MINUTES. THE RESIDUE (0.146 G.) WAS DISTILLED (0.01 MM, 125^o) TO GIVE A CLEAR OIL, WHICH WAS IDENTICAL TO CRIWELLINE METHINE (BY T.L.C.). THE RADIOACTIVITY OF THE METHINE WAS DETERMINED TO BE 1.01 DPM/MMOLE.

6-PHENYLPIPERONYL ALCOHOL

CRIWELLINE METHINE (0.160 G., 1.01×10^6 DPM/MMOLE) WAS DISSOLVED IN A SOLUTION OF 50 ML. OF 0.025 SODIUM METHOXIDE IN METHANOL AND THE SOLUTION WAS ALLOWED TO STAND AT ROOM TEMPERATURE FOR 24 HOURS. THE BASIC SOLUTION WAS NEUTRALIZED WITH TWO DROPS OF GLACIAL ACETIC ACID AND THE SOLVENTS WERE REMOVED UNDER REDUCED PRESSURE. THE RESIDUE WAS DISSOLVED IN 1 N HYDROCHLORIC ACID AND THE ACID SOLUTION WAS EXTRACTED THREE TIMES WITH ETHER. THE ETHER SOLUTIONS WERE DRIED OVER ANHYDROUS POTASSIUM CARBONATE AND EVAPORATED TO DRYNESS. THE RESIDUE (0.105 G.) WAS SUBLIMED (100^o, 0.01 MM) TO GIVE PRISMS: M.P.

99-100°; 1.02×10^6 DPM/MMOLE.

6-PHENYLPIPERONYLIC ACID

A SOLUTION OF 0.085 G. OF 6-PHENYLPIPERONYL ALCOHOL (1.02×10^6 DPM/MMOLE) IN 5 ML. OF T-BUTYL ALCOHOL WAS ADDED TO 10 ML. OF WATER CONTAINING 0.210 G. OF POTASSIUM PERMANGANATE. AFTER ONE HOUR AT ROOM TEMPERATURE THE SOLUTION WAS COMPLETELY BROWN, AND 3 ML. OF 20% SODIUM HYDROXIDE WAS ADDED TO PRECIPITATE THE HYDRATED MANGANESE DIOXIDE. THE INORGANIC SALTS WERE REMOVED BY FILTRATION THROUGH CELITE AND THE FILTRATE WAS MADE STRONGLY ACIDIC ($\text{PH} < 1$) WITH CONCENTRATED HYDROCHLORIC ACID. THE RESULTING PRECIPITATE WAS FILTERED AND WASHED WITH 1 N HYDROCHLORIC ACID. THE 6-PHENYLPIPERONYLIC ACID WAS SUBLIMED TO GIVE PRISMS: M.P. 215-216°; 3.36×10^4 DPM/MMOLE.

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