

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
SPONSORED PROJECT INITIATION

AGS

Date: 4/19/78

Project Title: Natural Anti-Tumor Agents form the Senecioneae

See G-33-P02

Project No: G-33-635

Project Director: Dr. Leon H. Zalkow

Sponsor: DHEW/PHS/NIH - National Cancer Institute; Bethesda, MD 20014

Agreement Period: From 4/1/78 Until 3/31/79 (01 year)

Type Agreement: Grant No. 1 R01 CA23277-01

Amount: \$40,081 New PHS Funds (G-33-635)
7,502 GIT Contribution (G-33-323)
\$47,583 Total

Reports Required: Annual Progress Reports with Continuation Applications
Terminal Progress Report upon Grant Expiration

Sponsor Contact Person (s):

Technical Matters

Moreshwar V. Nadkarni, Ph.D.
Division of Cancer Research Resources
and Centers
National Cancer Institute
Bethesda, MD 20014

Contractual Matters

(thru OCA)
Ms. Marian Focke
Grants Management Specialist
National Cancer Institute
Bethesda, MD 20014
Phone: (301) 496-7444

Defense Priority Rating: None

Assigned to: Chemistry (School/Laboratory)

COPIES TO:

Project Director
Division Chief (EES)
School/Laboratory Director
Dean/Director-EES
Accounting Office
Procurement Office
Security Coordinator (OCA)
 Reports Coordinator (OCA)

Library, Technical Reports Section
EES Information Office
EES Reports & Procedures
Project File (OCA)
Project Code (GTRI)
Other _____

GEORGIA INSTITUTE OF TECHNOLOGY
OFFICE OF CONTRACT ADMINISTRATION
SPONSORED PROJECT TERMINATION

Date: May 23, 1979

Project Title: Natural Anti-Tumor Agents From the Senecioneae

Project No: G-33-635

Project Director: Dr. Leon H. Zalkow

Sponsor: DHEW/PHS/NIH National Cancer Institute

Effective Termination Date: 3/31/79 (end of 01 Year)

Clearance of Accounting Charges: 3/31/79 for 01 Year

Grant/Contract Closeout Actions Remaining:

TERMINATED

- Final Invoice and Closing Documents
- Final Fiscal Report
- Final Report of Inventions
- Govt. Property Inventory & Related Certificate
- Classified Material Certificate
- Other Annual Report of Expenditures due by 6/30/79

NOTE: FOLLOW-ON PROJECT (02 YEAR) is G-33-P02.

Assigned to: Chemistry (School/Laboratory)

COPIES TO:

Project Director
Division Chief (EES)
School/Laboratory Director
Dean/Director—EES
Accounting Office
Procurement Office
Security Coordinator (OCA)
Reports Coordinator (OCA)

Library, Technical Reports Section
Office of Computing Services
Director, Physical Plant
EES Information Office
Project File (OCA)
Project Code (GTRI)
Other _____

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

REVIEW GROUP SSS	TYPE 5	PROGRAM R01	GRANT NUMBER (INSERT ON ALL PAGES) CA23277-02
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**APPLICATION
FOR CONTINUATION GRANT**

TOTAL PROJECT PERIOD	
FROM: 04/01/78	THROUGH: 03/31/81
REQUESTED BUDGET PERIOD	
FROM: 04/01/79	THROUGH: 03/31/80

TO BE VERIFIED BY APPLICANT. CHECK INFORMATION IN ITEMS 1 THROUGH 6. IF INCORRECT, FURNISH CORRECT INFORMATION IN ITEM 13.

1. TITLE NATURAL ANTITUMOR AGENTS FROM THE SENECEIONEAE		
2A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Name and Address, Street, City, State, Zip Code) ZALKOW, LEON H GEORGIA INST OF TECHNOLOGY 225 NORTH AVENUE, N W ATLANTA, GA 30332	4. APPLICANT ORGANIZATION (Name and Address, Street, City, State, Zip Code) GEORGIA INSTITUTE OF TECHNOLOGY 225 NORTH AVENUE, N W ATLANTA, GA 30332	
2B. DEGREE PHD	2C. SOCIAL SECURITY NO. 255-36-9515	5. PHS ACCOUNT NUMBER 1586 002023A1
2D. DEPARTMENT, SERVICE, LABORATORY OR EQUIVALENT SCHOOL OF CHEMISTRY	6. TITLE AND ADDRESS OF OFFICIAL IN BUSINESS OFFICE OF APPLICANT ORGANIZATION DIRECTOR OF FINANCIAL AFFAIRS GEORGIA INSTITUTE OF TECHNOLOGY 225 NORTH AVENUE, N W ATLANTA, GA 30332	
2E. MAJOR SUBDIVISION COLL OF SCIS & LIBERAL STUDIES		
3. ORGANIZATIONAL COMPONENT TO RECEIVE CREDIT FOR INSTITUTIONAL GRANT PURPOSES 20 OTHER		

COMPLETE THE FOLLOWING (See Instructions)

7. RESEARCH INVOLVING HUMAN SUBJECTS (See Instructions) <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES APPROVED: _____ DATE _____	8. INVENTION CERTIFICATION (See Instructions) <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES-NOT PREVIOUSLY REPORTED <input type="checkbox"/> YES-PREVIOUSLY REPORTED	
9. PERFORMANCE SITE (S) Georgia Institute of Technology 225 North Avenue, N. W. Atlanta, Georgia 30332	TELEPHONE INFORMATION	
	11A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (ITEM 2A)	AREA CODE TELE. NO. & EXT. 404 894-4045
	11B. NAME OF BUSINESS OFFICIAL (ITEM 6) Frank H. Huff	404 894-4622
	11C. NAME AND TITLE OF ADMINISTRATIVE OFFICIAL (ITEM 15B) J. G. Bishop, Jr. Grants & Contracts Off.	404 894-4814
10. DIRECT COSTS REQUESTED FOR BUDGET PERIOD \$26,161	12B. COUNTY OF APPLICANT ORGANIZATION SHOWN IN ITEM 4 Fulton	
12A. CONGRESSIONAL DISTRICT OF APPLICANT ORGANIZATION SHOWN IN ITEM 4 5th Congressional District		

13. USE THIS SPACE FOR CORRECTIONS TO ITEMS 1 THROUGH 6. INDICATE THE NUMBER(S) WHERE ANSWER(S) APPLY
2E College of Sciences and Liberal Studies

13A RECOMBINANT DNA RESEARCH [X]NO []YES (IF YES, UPDATED MUA REQUIRED)

14. CERTIFICATION AND ACCEPTANCE. WE, THE UNDERSIGNED, CERTIFY THAT THE STATEMENTS HEREIN ARE TRUE AND COMPLETE TO THE BEST OF OUR KNOWLEDGE AND ACCEPT, AS TO ANY GRANT AWARDED, THE OBLIGATION TO COMPLY WITH PUBLIC HEALTH SERVICE TERMS AND CONDITIONS IN EFFECT AT THE TIME OF THE AWARD.

SIGNATURES (Signatures required on original copy only. Use ink. "Per" signatures not acceptable.)	15A. PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR	DATE
	15B. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION	DATE 01/26/79

RETURN COMPLETED APPLICATION TO PHS AS SOON AS POSSIBLE:

SECTION II

SECTION II—BUDGET (USUALLY 12 MONTHS) FROM 4/1/79 THROUGH 3/31/80 GRANT NUMBER CA 23277-02

A. ITEMIZE DIRECT COSTS REQUESTED FOR NEXT BUDGET PERIOD

PERSONNEL		TIME OR EFFORT %/HRS. (c)	SALARY REQUESTED (d)	FRINGE BENEFITS (See Instructions) (e)	TOTAL (f)
NAME (Last, First, Initial) (a)	TITLE OF POSITION (b)				
ZALKOW, LEON H.	PRINCIPAL INVESTIGATOR	12.5%			
GELBAUM, LESLIE	Research Scientist	100%			
Subtotals			\$	\$	
(Indicate cost of each item listed below) TOTAL (Columns (d) and (e))					\$ 21,131
CONSULTANT COSTS (See Instructions)					\$
EQUIPMENT					
					\$
SUPPLIES Chemicals, Consumable Supplies, Solvents, Chromatograph Accessories, etc.					
					\$ 2,080
TRAVEL	DOMESTIC	To attend scientific meeting			\$ 750
	FOREIGN				\$
PATIENT COSTS (See instructions)					
					\$
ALTERATIONS AND RENOVATIONS					\$
OTHER EXPENSES (Itemize) Plant collecting, grinding, handling & shipping					
					\$ 2,200
TOTAL DIRECT COST (Enter on Page 1, Item 10)					\$ 26,161

INDIRECT COST (See Instructions) 76% S&W* % TDC* Date of DHEW Agreement: July 11, 1978 Not Requested Under negotiation with:

SECTION III

SECTION III—FISCAL DATA FOR
CURRENT BUDGET PERIOD
(USUALLY 12 MONTHS)

FROM	THROUGH	GRANT NUMBER
April 1, 1978	March 31, 1979	CA 23277-02

The following pertains to your CURRENT PHS budget. Do not include cost sharing funds. This information in conjunction with that provided on Page 2 will be used in determining the amount of support for the NEXT budget period.

A. BUDGET CATEGORIES		CURRENT BUDGET (As approved by awarding unit) (1)	ACTUAL EXPENDITURES THRU <u>12/31/78</u> (Insert Date) (2)	ESTIMATED ADDITIONAL EXPENDITURES AND OBLIGATIONS FOR REMAINDER OF CURRENT BUDGET PERIOD (3)	TOTAL ESTIMATED EXPENDITURES AND OBLIGATIONS (Col. 2 plus Col. 3) (4)	ESTIMATED UNOBLIGATED BALANCE (Subtract Col. 4 from Col. 1) (5)
Personnel (Salaries)		18,230	13,692	4,538	18,230	0
Fringe Benefits		1,705	1,073	632	1,705	0
Consultant Costs		--	--	--	--	--
Equipment		3,000	3,000	0	3,000	0
Supplies		2,000	587	1,413	2,000	0
TRAVEL	Domestic	750	750	0	750	0
	Foreign	--	--	--	--	--
Patient Costs		--	--	--	--	--
Alterations and Renovations		--	--	--	--	--
Other		2,000	619	1,381	2,000	0
Total Direct Costs		27,585	19,721	7,964	27,685	0
Indirect Costs (If included in award)		12,396	10,406	1,990	12,396	0
TOTALS →		\$40,081	\$30,127	\$ 9,954	\$40,081	\$ 0

Use space below to:

- B. List all items of equipment purchased or expected to be purchased during this budget period which have a unit cost of \$1000 or more.
C. Explain any significant balance or deficit shown in any category of Column 5.
D. List all other research support for Principal Investigator by source, project title, and annual amount.

B. A total of \$3,619 (\$3,000 from original equipment budget and \$619 transferred to equipment category from other expenses) was used as part of a total purchase of \$11,000 for a Waters 500 Preparative Liquid Chromatograph.

We expect to spend an additional \$2,000 from this grant for partial payment (total cost \$3,100) of a Waters Model R401 differential diffractometer for a liquid chromatograph.

APPLICANT: REPEAT GRANT NUMBER SHOWN ON PAGE 1 →		GRANT NUMBER	
SECTION IV—SUMMARY PROGRESS REPORT		CA23277-02	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR (Last, First, Initial)		PERIOD COVERED BY THIS REPORT	
Zalkow, Leon H.		FROM	THROUGH
NAME OF ORGANIZATION		4/1/78	1/1/79
TITLE (Repeat title shown in Item 1 on first page)			
Natural Antitumor Agents from the Senecioneae			

- List publications: (a) published and not previously reported; (b) in press. Provide five reprints if not previously submitted.
- List all additions and deletions in professional personnel and any changes in effort.
- Progress Report. (See Instructions)

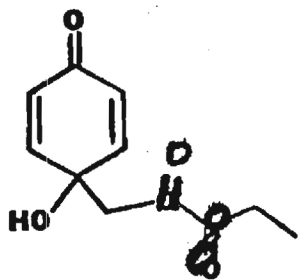
- L. Gelbaum and L. H. Zalkow, "Secondary Plant Metabolites from *Senecio smallii*." 30th Southeastern Regional Meeting, American Chemical Society, Savannah, Georgia Nov. 8-10, 1978.
- During the period covered, the following personnel devoted the indicated amounts of time. There will be no change except that Dr. H. Deutsch will not continue on this project.
 Dr. L. Gelbaum, Research Scientist, 100% time.
 Dr. H. Deutsch, Research Scientist, 25% time.
 Ms. S. Bonetti, B.S., technician, 50% time.
- During the period April 1, 1978 - Jan. 1, 1979, we have worked on the extracts from *Senecio smallii* and *Crotalaria spectabilis*. The extracts of these plants have been submitted for screening by the National Cancer Institute (NCI). Preliminary reports indicate that the 95% ethanol extract from *S. smallii* showed the activity indicated below:

Test System	Toxd. Surv.	Sex	Dose	T/C
PS	06/06	M	400	132
"	"	M	200	122
"	"	M	100	120
"	"	M	50	107
"	06/06	F	600	129
"	"	F	400	128
"	"	F	265	133
"	"	F	175	132
KB	—	—	—	2.7 X 10(1)

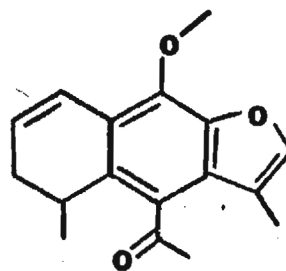
The aqueous methanol partition from the plant further concentrated the active component as shown by the KB screen value of $2.8 \times 10(0)$. Further separation and screening are in progress.

By high performance liquid chromatography (HPLC) we have thus far isolated and determined the structures of the following compounds from *S. smallii*: ethyl-1-hydroxy-4-oxo-2,5-cyclohexadiene-1-acetate (1), 14-oxo-1,2-dehydro-cacalol methyl ether (2), and the pyrrolizidine alkaloids senecionine (3), senkirkine (4), and retrorsine (5). Very efficient means have been developed for the separation of polar compounds such as pyrrolizidine alkaloids on reverse phase columns using HPLC and we have developed one of the most efficient laboratories in the country for separation of natural products by HPLC.

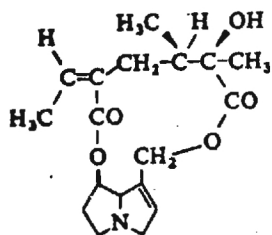
A large quantity of *Crotalaria spectabilis* seeds were collected in south Georgia and over 100 g of the pyrrolizidine alkaloid monocrotaline (6) was isolated from these seeds. Hydrolysis of this alkaloid, led in good yield to the necine base retronecine (7) which is being used in the synthesis of semi-



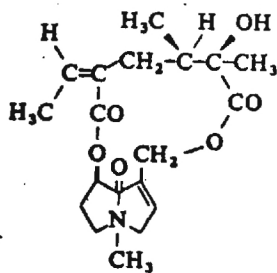
1



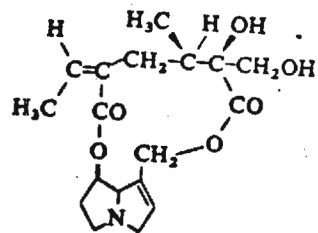
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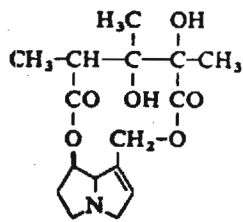
3



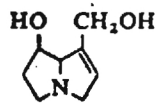
4



5



6



7

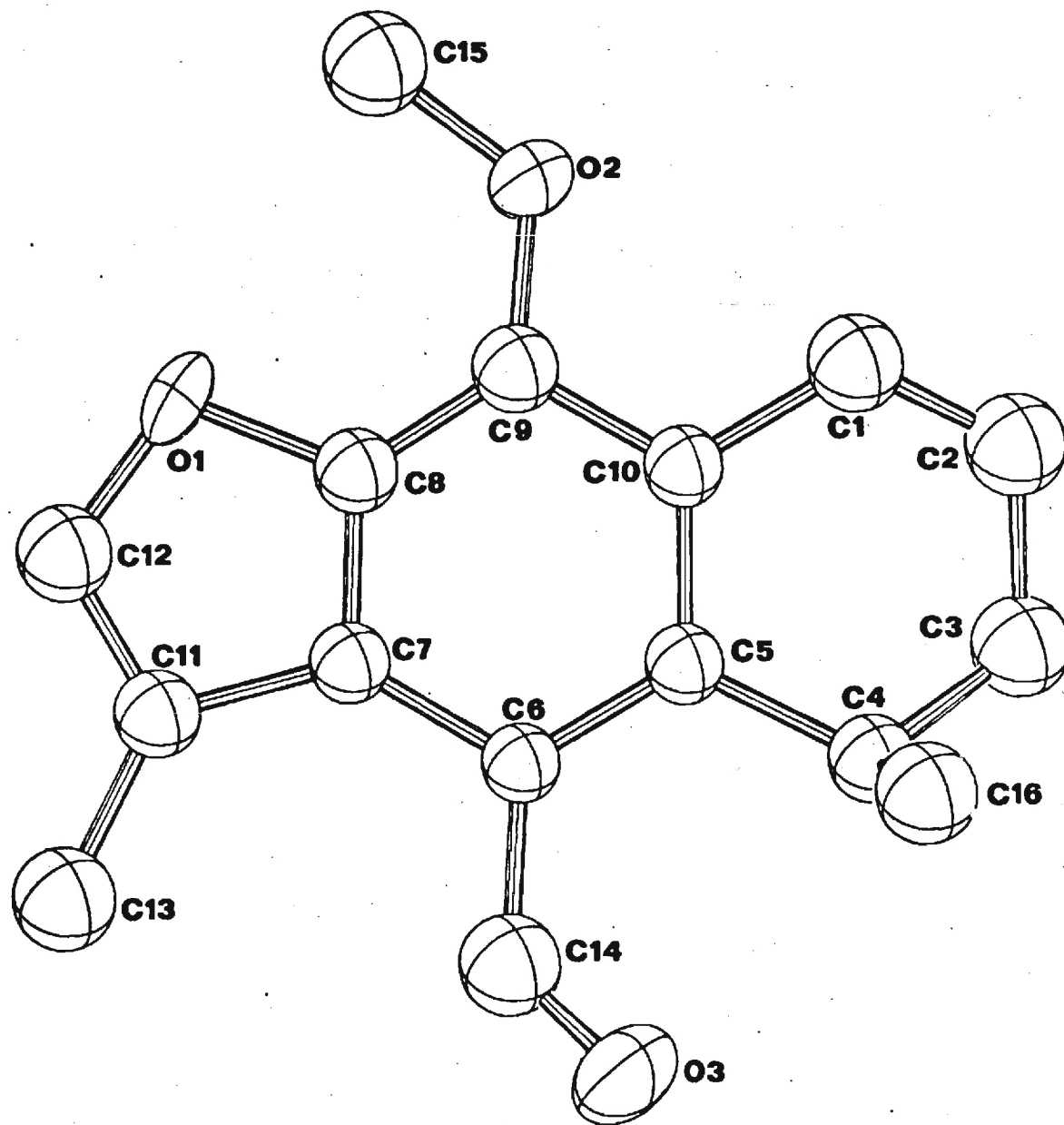


Figure I

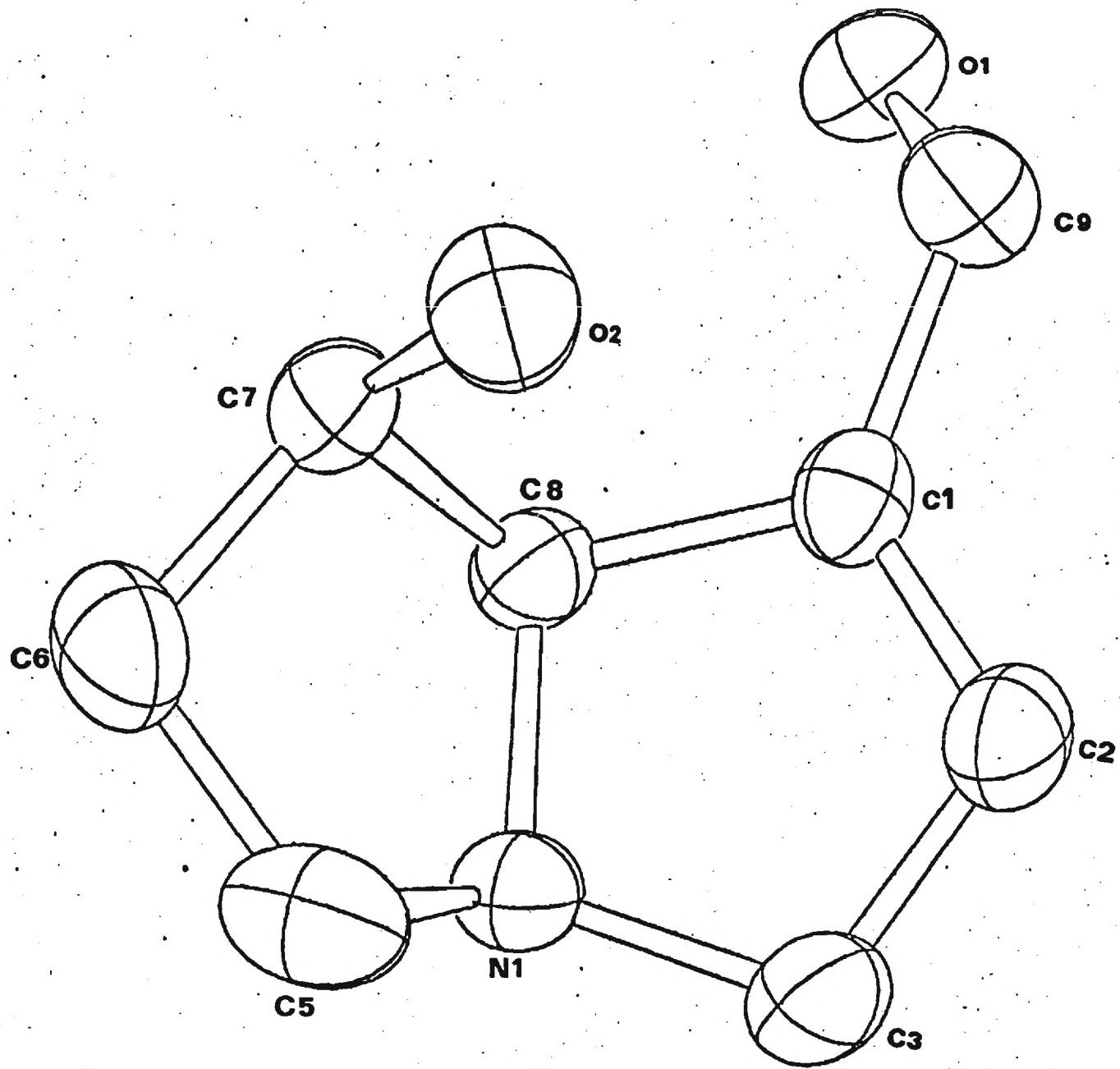


Figure II

3. (Continued)

synthetic pyrrolizidine alkaloids. In this synthetic work it is anticipated that increased activity over the purely natural active pyrrolizidine alkaloids such as indicine N-oxide will be realized by a study of structure-activity relationships.

During this period we have begun a compilation of ^{13}C NMR data on pyrrolizidine alkaloids which allows rapid structural and stereochemical assignments. Likewise, we have utilized single crystal x-ray analysis routinely when suitable crystals were available and structures 2 and 7 were arrived at by this method. Figures I and II show the computer drawn structures of 2 and 7 respectively as arrived at from the x-ray data.

During the next grant period we expect to continue work on the above mentioned plants and, in addition, we expect to initiate work on the following plants of the Senecio genus as recommended by Dr. T. M. Barkley of Kansas State University:

Section AUREI

Senecio pseud aureus
Senecio dimorphophyllus
Senecio streptanthifolius

Section LOBATI

Senecio multilobatus

Section TOMENTOSI

Senecio werneriaefolius
Senecio canus

Section LUGENTES

Senecio atratus
Senecio wootonii

Section INTEGERRIMI

Senecio intergerriimus

Section APLECTENTES

Senecio amplectens
Senecio bigelovii

Section SUFFRUTICOSI

Senecio douglasii
Senecio spartioides

Section TRIANGULARES

Senecio fremontii
Senecio triangularis
Senecio eremophilus

The undersigned agrees to accept responsibility for the scientific and technical conduct of the project and for provision of required progress reports if a grant is awarded as the result of this application.

1/24/79
 Date

✓ Principal Investigator _____

Texts: Horowitz and Sahni, Fundamentals of Data Structures
Knuth, The Art of Computer Programming, Vol. 1

Remedial Course: ICS 3113

Computer Systems

Knowledge of hardware and software components of digital computer systems including system architecture and organization, input/output, data representation, storage interrupts, parallel processing, microprogramming, minicomputers, and basic systems software such as language processors and multiprogramming operating systems.

Texts: Bell and Newell, Computer Structures: Readings and Examples
Freeman, Software Systems Principles

Remedial Course: ICS 3705