

# 序

新千年的第一个春天，欣逢黄量教授 80 岁寿辰，特编纂了此论文集作为寿礼以表示景仰之情。此文集概括了黄量教授学术上的成就，也记载了她在科研工作上不断攀登和求索中为我国的药学事业所作出的卓越贡献。

黄量教授 1920 年 5 月生于上海，1942 年毕业于上海圣约翰大学化学系。先后在上海生化制药厂、重庆中央工业试验所、上海医学院和重庆大学从事研究和教学工作。1946 年赴美国康奈尔大学深造，1949 年获化学博士学位。1949~1956 年先后在美国布林莫尔大学、康奈尔大学、韦恩大学和衣阿华大学从事有机化学理论、有机合成、天然产物结构测定等研究工作，显现出杰出的才能，受到各实验室知名教授的赞赏。

1956 年黄量教授怀着一颗献身新中国建设事业的赤子之心，放弃在国外优裕的工作和生活条件，毅然举家回到阔别十年的祖国。1957 年起历任中国医学科学院药物研究所副研究员、研究员，药物合成室主任。1980 年被选为中国科学院学部委员（院士）。曾先后担任过中国化学会第 21，22 两届常务理事，中国癌症研究基金会副理事长，全国肿瘤防治研究领导小组及全国计划生育科技专题委员会顾问等职，及兼任北京医科大学天然药物及仿生药物国家重点实验室副主任委员。1984 年被选为发展中国家的国际化学会（IUCD）委员。

黄量教授有很深的学术造诣，但她四十年来仍然好学不倦，不断拓宽自己的知识领域。她原来专业是有机化学，对药物化学中有关疾病的病理、药理等方面的知识并不熟悉，但她刻苦钻研，广泛阅读有关方面的书籍，并亲自参加药物临床试验等实践活动，因此她很快就成为国内知名的药物化学家。

黄量教授回国 40 年来为我国的药物研究事业作出了卓越的贡献，取得了多项开创性成果。50 年代我国治疗高血压的药物萝芙木总碱及其有效成分利血平均需要从国外进口。为研究国产萝芙木是否具有降血压作用，卫生部组织了全国协作进行研究，药物研究所几位年轻科研人员在黄量教授的指导下，率先分离出有效成分利血平，并研制出新中国第一个降血压药物“降压灵”。

在抗肿瘤药物研究中，黄量教授与药理等学科合作，先后研制出治疗精原细胞瘤的 N-甲酰溶肉瘤素，治疗急、慢性粒细胞白血病的三尖杉酯碱、靛玉红、甲异靛等药物。分别获得卫生部二等甲级成果奖，国家科技进步一等奖，国家发明二等奖。

为研制肿瘤化学预防药物，她和本所药理室及中国医学科学院肿瘤研究所合作，设计并合成了维 A 酸的衍生物——维酸酯，具有防止癌前病变的药物。并获得国家科技进步三等奖。

她还指导过抗病毒药物的研究工作，研制出我国第一个抗病毒合成新药酞丁胺，用于治疗单纯疱疹、带状疱疹、尖锐湿疣等病毒性皮肤病，并获国家发明二等奖。

在计划生育药物的研究中，为解决棉酚的毒副反应问题，黄量承担了(+)、(-)棉酚的拆分工作，在世界上优先于英、法、印度等三国受 WHO 资助进行同样工作的实验室，取得了高光学纯度的(+)和(-)棉酚，受到了 WHO 的赞誉。

80 年代后期黄量潜心于中药黄皮的研究工作，从黄皮的水浸膏中分得 7 种

有生理活性的酰胺类生物碱。在深入的理论分析基础上还完成了这些活性成分各光学异构体的合成。此项目被列为“九五”重大项目“手性药物的化学与生物学研究”的一个子课题，并该重大项目的首席科学家之一。

截至 1999 年底，黄量教授共发表论文 107 篇，为有关专著撰写“旋光谱及圆二色谱”、“肿瘤化学治疗中合成药物的进展和动向”等专题文章。1988 年出版了她和于德泉编著的“紫外光谱在有机化学中的应用”一书，受到广泛的欢迎。为国外书刊撰写的文章有“天然产物及其对中国人民健康的贡献”（载于联合国教科文组织的《科学对社会的贡献》杂志），“三尖杉生物碱”（载于美国学术出版社出版的《生物碱》第 23 卷），“药物化学在中国的进展”（载于美国出版的《综合药物化学》）。她还担任了“医学百科全书”中的“药物学和药理学”分册的主编。黄量教授曾多次应邀参加国际会议，做了“男用避孕药——棉酚”、“化学对中国计划生育的贡献”、“中草药中有生物活性的黄酮”等报告。

由于黄量教授在科学研究上取得的成就和为我国药学事业作出的贡献，1998 年被授予“何梁何利科学进步奖”。

黄量十分重视科技人才的培养，为国家培养了一批药学专家、科技骨干，亲自指导了 30 多名硕士和博士研究生的学习。她治学严谨，好学不倦，工作刻苦的精神影响和教育了学生。“严师出高徒”，经她严格要求、精心指导下培养的学生在国内外的学习和工作中均有良好表现。

黄量教授不仅在学术上有很高造诣，而且品德高尚，为人耿直，对于不正、不公之事敢于仗义执言，这些赢得了大家的赞赏和尊敬。党和国家对黄量教授的辛勤劳动和工作成绩给予了高度评价，先后被评为全国三八红旗手（1959）、北京市先进工作者，并当选为第五、六、七届全国政协委员。

黄量教授的治学和为人我们树立了一个学习的榜样。

赵 知 中

2000 年 3 月



黃 量

胸怀超泰西  
碩果压枝低  
千禧八旬寿  
期頤信可期

梁曉天 融书



千禧年春

## RÉSUMÉ

Huang Liang, an organic and medicinal chemist, was born in 1920 in Shanghai. She received her B.S. degree in chemistry in 1942 from St. John's University in Shanghai, and her Ph.D. in organic chemistry from Cornell University in the United States in 1949 working with Prof. A. T. Blomquist. She performed her further research work at Cornell University, Bryn Mawr College (Prof. E. Berliner), Wayne State University (Prof. C. Djerassi) and Iowa State University (Prof. E. Wenkert) on organic synthesis, physical organic chemistry, and natural products.

In 1956, Prof. Huang returned with her husband Liu Jing Xu and daughter to her home country, China. In the following year, she joined the Department of Materia Medica of the Central Institute of Health, which was later reorganized to form the Institute of Materia Medica of the Chinese Academy of Medical Sciences in 1958. She was the director of the Department of Organic Synthesis of the institute from 1960 to 1983 and has been a full professor since 1964. She was elected as Member of the Chinese Academy of Sciences in 1980.

During her research career, Prof. Huang has made substantial contribution. Her research areas concern the search for new anticancer, and antiviral drug, contraceptives and synthesis and modification of biologically active natural products. Currently her research interest is in chiral drugs. Eight of the research projects from her group have been awarded either the National Progress in Science and Technology Award or the National Invention Award. In 1998, she received HLHL Prize in medical science.

Prof. Huang Liang is the author of more than 100 research publications. She was the chief editor of the Volume of "Pharmaceutical Science and Pharmacology" in the "Chinese Encyclopedia of Medical Sciences" and a member of the international advisory board of the six-volume "Comprehensive Medicinal Chemistry".

Prof. Huang has demonstrated boundless enthusiasm in guidance her graduate students. Up to 1999 the thirty- two Ph.D and M.S. graduate students whom she has supervised all are doing well in their own right.

# 目 录

## 一. 有机化学理论及化学反应的研究

1. Many-membered carbon rings.IV. Synthesis of cyclononyne and cyclodecyne .....	1
2. Many-membered carbon rings VI. Unsaturated nine-membered cyclic hydrocarbons...	2
3. Many-membered carbon rings VII. Cyclooctyne .....	7
4. The hydrolysis of substituted ethyl p-biphenyl- carboxylates .....	9
5. An approach to ring E of reserpinoid substances .....	12
6. 高效酰化催化剂——4-二甲基吡啶的合成.....	19
7. 异三尖杉酯碱的合成及异构体的分离.....	22
8. S-及 R-对甲苯亚磷酸 I-薄荷醇酯的合成及两异构体的分离.....	23
9. 瑞氏(Reformatsky)反应制备 $\alpha$ -烷氧基- $\beta$ -羟基羧酸酯 .....	26
10. A novel free radical rearrangement .....	28
11. Solvent participation of Wittig olefination reaction in methanol .....	30
12. Diels-Alder Reactions of 3-carboethoxy- and 3-Carbonitrile-2-Cyclohexen-1-one.....	32
13. Intramolecular Induction of Asymmetric Darzen's Condensation of Aldehydes with Chiral $\alpha$ -Chloroacetate.....	34
14. (+)-1S, 2R, 5S-8- $\beta$ -萘基薄荷醇的合成.....	36

## 二. 抗肿瘤、抗病毒及防癌药物的研究

1. 抗癌药研究 I. 谷氨酰胺衍生物的合成.....	42
2. 抗病毒药物的研究 III. 芳香 $\alpha$ -酮醛的合成.....	48
3. 抗病毒药物的研究 II. 乙酰苯衍生物的合成.....	61
4. 抗肿瘤药物的研究 V. 谷氨酰胺衍生物的合成.....	66
5. The synthesis and antitumor activity of kethoxal bis-thiosemicarbazone and its related compounds.....	76
6. 抗肿瘤及抗病毒药物的研究 IV. $\alpha$ -酮醛与肼、羟胺及芳胺缩合化合物的合成.....	87
7. 抗肿瘤及抗病毒药物的研究 V. $\beta$ -乙氧基- $\alpha$ -正丁酮醛双缩氨硫脲类似物的合成.....	99
8. 霉变食物中新亚硝胺: N-3-甲基丁基-N-1-甲基丙酮基亚硝胺.....	105
9. A new N-nitroso compound, N-3- methylbutyl N-1- methylacetyl- nitrosamine, in corn-bread inoculated with fungi.....	112
10. 农吉利抗癌有效成分的分离及其衍生物的合成.....	120
11. 抗肿瘤及抗病毒药物的研究 VI. 消旋 $\beta$ -邻苯二甲酰亚氨- $\alpha$ -正丁酮醛衍生物的合成.....	126
12. 防癌药物的研究—维生素甲酸衍生物的合成.....	131
13. N-3-甲基丁基-N-1'-甲基丙酮基亚硝胺的合成.....	140
14. 24 个新维甲酸衍生物对人食管癌细胞株克隆三(Eca109-C <sub>3</sub> )增殖的影响...	145
15. N, N-双( $\beta$ -氯乙基)N', N"- 二(乙氧羰-[C <sup>14</sup> ]甲基)-磷三酰胺(I)的合成.....	151

16. 抗白血病药物靛玉红的 $N_1$ 取代物的合成·····	154
17. 二胺及其衍生物对体内小鼠 S180 鸟氨酸脱羧酶活性的影响·····	159
18. 抗白血病药物靛玉红以及靛蓝和异靛蓝衍生物的合成·····	164
19. 中药青黛中几种微量成分的研究. I. 吡啶并[2,1-b]喹唑啉-6, 12-二酮和青黛酮的分离、结构鉴定及合成·····	170
20. 三尖杉酯碱的半合成研究·····	177
21. 三尖杉酯碱的半合成研究·····	178
22. 半合成差向异构体三尖杉酯碱和表三尖杉酯碱的分离和鉴定·····	180
23. 新抗癌有效成分海南粗榧内酯(Hainanolide)结构的研究·····	184
24. 三尖杉酯碱的半合成·····	189
25. Partial Synthesis of Harringtonine·····	199
26. 海南粗榧中的微量生物碱·····	212
27. 半合成差向异构体——三尖杉酯碱与表三尖杉碱的制备型高压液相色谱分离及鉴定·····	217
28. 几种三尖杉酯碱衍生物的合成·····	219
29. 脱氧三尖杉酯碱和高三尖酯碱的立体专一性合成·····	223
30. 异三尖杉酯碱的合成及其异构体的分离·····	229
31. Study on the total synthesis of Hainanolide---construction of tricyclic intermediate (I) ·····	237
32. Study on the total synthesis of Hainanolide (II)—An unexpected hydroperoxide containing tricyclic skeleton·····	239
33. Study on the total synthesis of Hainanolide (III)—Unusual Diene Isomerization in a Diels-Alder reaction·····	241
34. Studies on the total synthesis of Hainanolide (IV)—Revising the stereochemistry of $C_{2a}$ -H and Introducing the two hydroxy Groups at $C_{3\beta}$ , $C_{4\alpha}$ positions·····	143
35. Chemical Studies on Decahydroacenaphthene Compounds—Studies on the Synthesis of Hainanolide -- Constuction of Tricycle Intermediate·····	245
36. Study on the total Synthesis of Hainanolide(II), Oxidation of the Tricyclic Alkenes with Singlet Oxygen·····	247

### 三. 天然产物的合成

1. Terpenoids, XI. Investigation of nine cactu species. Isolation of two new triterpenes, stellatogenin and machaeric acid·····	249
2. Tripenoids, XVII. The cactus triterpenes thurberogenin and stellatogenin·····	253
3. The constitution of the allooyhimbanes·····	260
4. The neutral constituents of the cactus Lophocereus Shottii·····	265
5. The stereochemistry of Reserpine, Deserpidine and related alkaloids·····	274
6. A dihydroresorcinol derivative·····	288
7. 黄皮叶中黄皮酰胺的分离、结构测定·····	291
8. Studies on the chemical constituents of Clausena Lansium (Lour) Skeels II·····	299
9. 黄皮叶化学成分的研究 II. 两个新的环酰胺化合物的结构·····	305

10. Three novel cyclic amides from Clausena Lansium.....	310
11. Asymmetric synthesis of (-)- dehydroclausenamide.....	316
12. Studies on the chemical constituents of Clausena Lansium (Lour.) Skeels III, The structural elucidation of homo- and Zeta-clausenamide .....	324
13. Studies on the chemical constituents of clausena Lansium (Lour.) Skeels IV, The structural elucidation of seco and secodemethyl clausenamide.....	326
14. Preliminary studies on the kinetic resolution of methyl erythro-phenylglycerate and methyl t-epoxycinnamate by PLE.....	328
15. 去甲原黄皮酰胺苏式异构体的最短合成路线.....	330
16. 缩丙酮-(R)-甘油醛加成物的缩酮交换.....	332
17. Study on the intramolecular cyclization through opening of epoxide I Cycliza- tion of N-methyl-N-benzoyl methylene-β-phenyl-α,β-epoxypropionamide in aprotic solvent.....	334
18. Study on the intramolecular cyclization through opening of epoxide II Ring closure of N-methyl-N-benzoyl-methylene-β-phenyl-α,β-epoxypropi- onamide in protic solvent.....	336
19. Asymmetric syntheses of stereoisomers of secodemethylclausenamide.....	338
20. Total synthesis of clausenamide.....	340
21. Synthesis of stereoisomers of secoclausenamide I and secodemethylclaus- enamide II .....	342
22. Total synthesis of neoclausenamide and its epimer.....	344
23. 黄皮酰胺的合成.....	346
24. An attempt to synthesize homo-clause- namide and zeta-clausenamide. Study of the intramolecular cyclization.....	350
25. Study of Intramolecular Cyclization of N-styryl-oxo-cinnamides II .....	353
26. 国产罗芙木成分的研究 I.....	355
27. 鸦胆子甙的化学结构研究.....	359
28. 氯霉素类似物-1-硝基苯-2-(N甲基,二氯乙酰氨基) 丙醇-1.....	363
29. 仙鹤草根芽中驱蜂虫成分鹤草酚的结构研究(简报) .....	366
30. 鹤草酚的结构研究.....	368
31. Quinolone alkaloids from Evodia Rutaecarpa Benth.....	378
32. 吴茱萸化学成分的研究.....	380
33. Quinolone alkaloids from Evodia Rutaecarpa.....	385
34. Studies on the Chemical Constituents of Evodia Rutaecarpa [Juss] Benth.....	389
35. 2-烷基取代喹诺酮的合成及生物活性.....	394
36. 2-烯基-4(1H)-喹诺酮的合成及生物活性研究.....	401
37. 毛茛甙全合成的研究.....	407
四. 抗孕药、甾类化合物和棉酚的研究	
1. 甾体同化激素的研究.....	414
2. 龙舌兰植物中甾体皂甙元的研究I. 番麻中甾族皂甙元的分离和鉴定.....	415

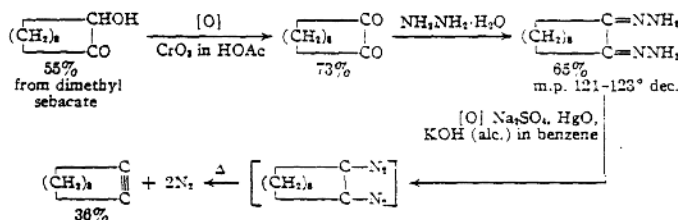


3. 龙舌兰植物中甾族皂甙元的研究II. 剑麻中甾族皂甙元的分离和鉴定·····	428
4. 龙舌兰属植物中甾族皂甙元的研究 III. 几种国产龙舌兰麻中甾族皂甙元的分离和鉴定·····	445
5. 环己酮19-去甲基双炔甾族化合物的合成·····	452
6. 长效避孕药——17 $\beta$ -甾醇酯的合成·····	459
7. 18-甲基炔诺酮中间体的拆分·····	464
8. 17- $\beta$ -甾醇酯胺-3的合成及其异物体分离鉴定·····	468
9. 由消旋棉酚拆分得(-)棉酚·····	471
10. Resolution of Racemic Gossypol ·····	472
11. 消旋棉酚拆分的研究 I.(S)-1-甲基苯乙胺缩(+)棉酚六乙酯的分离·····	474
12. Resolution of Racemic gossypol·····	480
13. Absolute Configuration of Gossypol·····	488
14. Selective inhibition of human immunodeficiency virus type 1 replication by the (-) but not the (+) enantiomer of gossypol·····	491
15. 消旋棉酚拆分的研究 II. 手性 $\alpha$ -甲基苯乙胺及 $\alpha$ -甲基苯胺为拆分剂·····	494
16. 消旋棉酚的拆分研究III. 胺缩棉酚理化性质的研究·····	500
17. 消旋棉酚的研究IV. 苏(-)或(+)-1-(对硝基苯基)-1,3-二羟苯基丙胺-2为拆分剂·····	507
18. Chiroptical Properties of stereoisomeric conjugated oximes·····	512
19. 棉酚及其相关化合物的分子力学和分子图形学研究·····	515
20. Anti-HIV-1 activity and cellular pharmacology of various analogs of gossypol·····	518
五. 专利·····	523
六. 专著·····	525
七. 附录·····	526
1. 按年序排列的论文目录(包括作者、论文题目、杂志、发表时间)·····	527
2. 获奖研究项目·····	534
3. 培养的研究生·····	535

# MANY-MEMBERED CARBON RINGS. IV. SYNTHESIS OF CYCLONONYNE AND CYCLODECYNE

Sir:

We have found that the synthesis of many-membered carbon rings containing an acetylenic group using the methods employed by Ruzicka in preparing cyclopentadecyne and cycloheptadecyne,<sup>1</sup> by Stoll in obtaining cycloheptadecyne-10-one,<sup>2</sup> and by Domin<sup>3</sup> in his presumed synthesis of cyclodecyne always seems to have afforded mixtures of cyclic acetylenes and isomeric allenes when applied to the nine- and ten-membered carbon rings. Thus, for example, dehydrohalogenation of 1-chlorocyclononene or dehalogenation of 1-bromo-2-chlorocyclodecene gave a mixture of  $C_9H_{14}$  and  $C_{10}H_{16}$  hydrocarbons, respectively, which upon ozonolysis yielded a mixture of suberic and azelaic acids or a



mixture of azelaic and sebacic acids. Further, the infrared spectrum of the  $C_{10}H_{16}$  hydrocarbon mixture showed a very weak absorption at  $4.55 \mu$  ( $\text{C}\equiv\text{C}$  stretching) and a much stronger absorption at  $5.16 \mu$  ( $\text{C}=\text{C}$  stretching).

However, we have obtained the cyclic  $C_9$  and  $C_{10}$  acetylenes employing a modification of a method developed by Curtius for synthesizing diaryl acetylenes.<sup>4</sup> The method as applied to the nine- and ten-membered carbocycles is illustrated by the synthesis of cyclodecyne from sebacoin.

The cyclic acetylenes ( $C_9$  and  $C_{10}$ ) as first isolated were found to contain small amounts of carbonyl compounds and saturated hydrocarbons but they were not contaminated with allenes or other unsaturated hydrocarbons. Final purification of the two acetylenes was achieved by chromatography through silica gel. Their purification was followed by means of infrared absorption spectra, refractive index measurements, and by quantitative catalytic hydrogenation.

Cyclodecyne was purified by chromatography through silica gel: b.p.  $203-204^\circ$  (740 mm.),  $n_D^{20}$  1.4903,  $d_4^{20}$  0.8975 (Anal. Calcd. for  $C_{10}H_{16}$ : C, 88.16; H, 11.84. Found: C, 88.30, 88.06; H, 11.78, 11.98). Quantitative reduction in acetic acid using Adams catalyst required 99-100% of

two molar equivalents of hydrogen. Ozonolysis gave only sebacic acid (37%), m.p.  $126-129^\circ$  after recrystallization and the mixed melting point with an authentic specimen of sebacic acid (m.p.  $129-131^\circ$ ) was  $126-129^\circ$ . The ozonolysis product was also characterized as sebacic acid by conversion to the bis-*p*-toluidide, m.p.  $198-200^\circ$  (cor.). Hydration of the acetylene with sulfuric acid and mercuric sulfate in acetic acid gave cyclodecanone, isolated as its semicarbazone, m.p.  $203.5-205.5^\circ$  (cor.). A mixed melting point with an authentic specimen showed no depression. The infrared spectrum of the unsaturated hydrocarbon (Fig. 1) showed characteristic absorption for  $\text{C}\equiv\text{C}$  at  $4.53 \mu$ .

Cyclononyne was purified by chromatography through silica gel: micro b.p.  $177-178^\circ$  (740 mm.),  $n_D^{20}$  1.4891,  $d_4^{20}$  0.8979. (Anal. Calcd. for  $C_9H_{14}$ : C, 88.45; H, 11.55. Found: C, 88.24; H, 11.64). Quantitative reduction in acetic acid using Adams catalyst required 102% of two molar equivalents of hydrogen. Hydration with sulfuric acid and mercuric sulfate in acetic acid gave cyclononanone, identified as its semicarbazone (m.p.  $179-180^\circ$ ). Mixed melting point with an authentic specimen showed no depression. Infrared spectrum of cyclononyne (Fig. 1) showed characteristic absorption for  $\text{C}\equiv\text{C}$  at  $4.54 \mu$ .

point with an authentic specimen showed no depression. Infrared spectrum of cyclononyne (Fig. 1) showed characteristic absorption for  $\text{C}\equiv\text{C}$  at  $4.54 \mu$ .

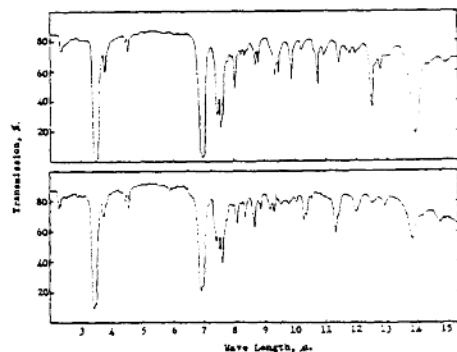


Fig. 1.—Upper curve infrared spectrum of cyclodecyne; lower curve infrared spectrum of cyclononyne.

Further details concerning these two cyclic acetylenes and the related cyclic *cis*- and *trans*-olefins will be presented as soon as possible in regular articles.

THE BAKER LABORATORY  
OF CHEMISTRY  
CORNELL UNIVERSITY  
ITHACA, NEW YORK

A. T. BLUMQUIST  
ROBERT E. BURGE, JR.  
LIANG HUANG LIU  
JAMES C. BOHRER  
ARTHUR C. SUCSY  
JOHN KLEIS

RECEIVED SEPTEMBER 14, 1951

- (1) L. Ruzicka, M. Hürbis and H. A. Boekenoggen, *Helv. Chim. Acta*, **16**, 498 (1933).
- (2) M. Stoll, J. Hultskamo and A. Rouve, *ibid.*, **31**, 543 (1948).
- (3) N. A. Domin, *J. Gen. Chem. (U.S.S.R.)*, **3**, 951 (1958); *Chem. Abstr.*, **53**, 1282 (1959).
- (4) T. Curtius, *Ber.*, **22**, 2161 (1889); T. Curtius and K. Thun, *J. prakt. Chem.*, [2] **44**, 168 (1891).

(CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY)

# Many-Membered Carbon Rings. VI. Unsaturated Nine-membered Cyclic Hydrocarbons<sup>1</sup>

BY A. T. BLOMQUIST, LIANG HUANG LIU<sup>2</sup> AND JAMES C. BOHRER<sup>3</sup>

RECEIVED JANUARY 21, 1952

The nine-membered cyclic hydrocarbons, cyclononyne, *cis*-cyclononene and *trans*-cyclononene, have been synthesized. The alkali-catalyzed oxidative decomposition of 1,2-cyclononanedione dihydrazone produced cyclononyne. Hydrogenation of cyclononyne over a palladium catalyst led to *cis*-cyclononene while reduction of the acetylene with sodium in liquid ammonia gave *trans*-cyclononene. *trans*-Cyclononene was also formed by the thermal decomposition of cyclononyltrimethylammonium hydroxide. The *trans*-olefin appears to be the labile form and to be strained. It is isomerized thermally, under acidic conditions, to *cis*-cyclononene and is reactive toward phenyl azide. Dehydration of cyclononanol with boiling phthalic anhydride gave a mixture of the *cis*- and *trans*-olefins, indicating that *trans*-cyclononene is probably less strained than *trans*-cyclodecene. The infrared spectra of several of the nine-membered carbocycles are given.

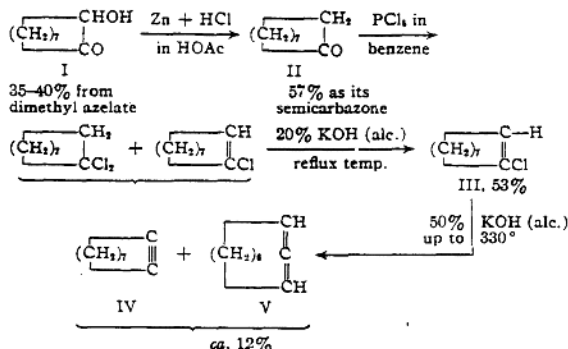
The preparation and properties of some simple unsaturated ten-membered cyclic hydrocarbons were described recently.<sup>1</sup> It was reported that cyclodecyne, free from its isomeric allene, could be obtained only by the oxidative decomposition of 1,2-cyclodecanedione dihydrazone. Also, chemical evidence was presented to support the view that both *cis* and *trans* forms of cyclodecene are probably strainless. This paper describes the synthesis of cyclononyne (IV), *cis*-cyclononene (XI) and *trans*-cyclononene (X). Evidence is also presented indicating that the *trans* form of cyclononene may be strained while the *cis* isomer is probably strainless.

Azeloin (I), obtained in improved yield (35–40%) by the method used to prepare sebacoins,<sup>1</sup> served as the starting carbocycle for all syntheses. Purification of the various nine-membered unsaturated hydrocarbons was frequently achieved through methods of chromatography while it was most convenient to follow these purifications by measurement of infrared spectra and refractive indices.

Cyclononyne (IV).—The first attempt to obtain this acetylene was by the dehydrohalogenation of 1-chlorocyclononene (III), a procedure applied successfully by Ruzicka, *et al.*, in the synthesis of cyclopentadecyne and cycloheptadecyne.<sup>4</sup> These experiments are summarized in the diagram which follows.

The product obtained by vigorous treatment of III with strong alcoholic potassium hydroxide solution was a hydrocarbon which absorbed two molar equivalents of hydrogen. That it was a mixture of approximately equal amounts of IV and V was indicated by ozonolysis which afforded roughly equal quantities of azelaic and suberic acids. The infrared spectrum of this product (IV + V) showed very weak absorption in the region charac-

teristic for  $\text{—C}\equiv\text{C—}$  (ca. 4.5  $\mu$ ) and stronger absorption around 5 $\mu$ , characteristic of  $\text{C}=\text{C}=\text{C}$ .

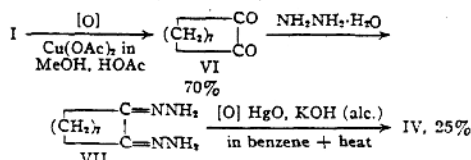


The molecular refractivity was found to be intermediate between the values calculated for IV and V.



Fig. 1.—Enantiomorphs of *trans*-cyclononene.

The alkali-catalyzed oxidative decomposition of 1,2-cyclononanedione dihydrazone (VII)<sup>5</sup> gave IV free from V. Following the route outlined below, pure IV was obtained in 25% yield from VII; final purification of distilled product was achieved by chromatographing through silica gel to constant refractive index ( $n_D^{20}$  1.4890).



Cupric acetate in acetic acid–methanol proved to be superior to the reagent chromium trioxide in acetic acid for the oxidation of I to VI.

(5) (a) A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 496; (b) T. Curtius and R. J. Kastner, *J. prakt. Chem.*, [2] 83, 215 (1913); (c) W. Schlenk and E. Bergmann, *Ann.*, 463, 71 (1928).

(1) For the preceding paper in this series see A. T. Blomquist, R. E. Burge, Jr., and A. C. Susay, *This Journal*, 74, 3636 (1952).

(2) Postdoctoral Research Fellow under the du Pont grant-in-aid, 1951–1952.

(3) Part of this paper is abstracted from a dissertation submitted by J. C. Bohrer in February, 1951, to the Graduate Faculty of Cornell University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(4) L. Ruzicka, M. Hürbin and H. A. Boekennoogen, *Helv. Chim. Acta*, 16, 498 (1933).

The infrared spectrum of IV and some of its other properties were reported earlier.<sup>6</sup> The sample of IV absorbed 102% of two molar equivalents of hydrogen upon quantitative reduction in acetic acid using Adams catalyst. It gave only azelaic acid upon ozonolysis and was converted to II when hydrated.

**trans-Cyclononene (X).**—This hydrocarbon has been obtained by the thermal decomposition of cyclononyltrimethylammonium hydroxide and by the reduction of IV with sodium in liquid ammonia.

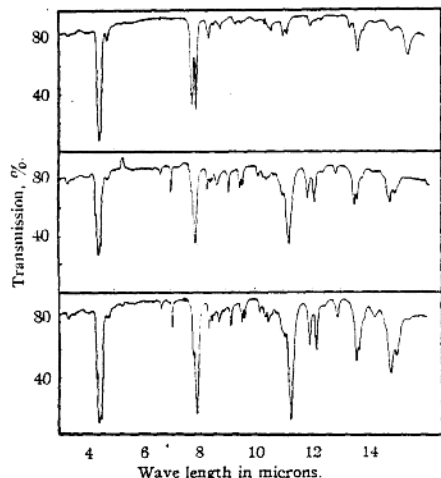


Fig. 2.—Infrared spectra: upper curve, cyclononane; middle curve, X from VIII; lower curve, X from reduction of IV with sodium in liquid ammonia.

The specimens of X obtained by the two methods showed practically the same refractive index,  $n_D^{20}$  1.4799 and 1.4800, respectively. The infrared spectra for the two samples also were in excellent agreement (Fig. 2), both spectra showing very strong absorption at 10.25  $\mu$ , characteristic of a *trans* C=C.

X absorbed 100.5% of one molar equivalent of hydrogen and gave only azelaic acid upon ozonolysis. When treated with phenyl azide according to Ziegler and Wilms,<sup>7</sup> X gave a crystalline solid adduct within 2–3 hours. Also following the procedure of Ziegler and Wilms, X was isomerized to XI when heated for 1.5 hours at 150° in the presence of a small amount of  $\beta$ -naphthalene-sulfonic acid. The infrared spectrum and other properties of the hydrocarbon, produced on isomerization, were in excellent agreement with those of XI. The infrared spectrum (Fig. 3) showed strong absorption in the 13.5–14.5  $\mu$  region (*cis* C=C) and no absorption at 10.25  $\mu$ . When treated with phenyl azide, the isomerized hydrocarbon showed no appreciable reaction after a period of two weeks.

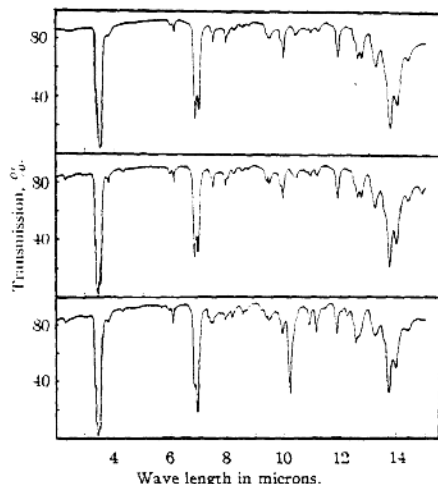
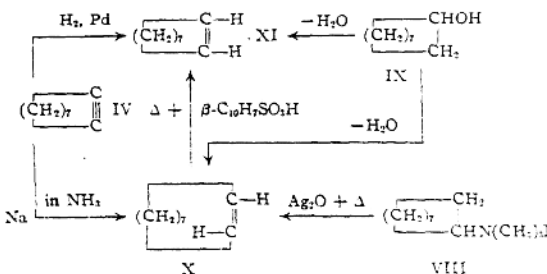


Fig. 3.—Infrared spectra: upper curve, XI from catalytic hydrogenation of IV; middle curve, XI from isomerization of X; lower curve, mixture of X and XI from dehydration of IX.

**cis-Cyclononene (XI).**—This hydrocarbon was produced by the selective catalytic hydrogenation of IV over a palladium catalyst supported on barium carbonate. The specimen of IV so obtained showed strong general absorption in the 13.5–14.5  $\mu$  region of the infrared and no absorption at 10.25  $\mu$  (Fig. 3). It absorbed 101% of one molar equivalent of hydrogen and gave only azelaic acid upon ozonolysis. When treated with phenyl azide there was no observable reaction; no crystalline adduct formed over a period of 4 weeks.

As mentioned earlier, XI was also obtained by the acid-catalyzed thermal isomerization of X.

Dehydration of cyclononanol (IX) with boiling phthalic anhydride afforded a mixture of X and XI as indicated by the infrared spectrum (Fig. 3). The interrelationship of the three hydrocarbons IV, X and XI is shown in the diagram below.



### Discussion

It is interesting to compare the properties of the *cis-trans* isomers of the eight-, nine- and ten-membered cyclic olefins.<sup>1,7</sup> It has been observed previously<sup>1</sup> that within a related series of hydrocarbons, both cyclic and open-chain, in which all the members are strainless there is a decrease in refrac-

(6) A. T. Blomquist, *et al.*, *This Journal*, **71**, 5510 (1951).

(7) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1939).

tive index and density in the order: acetylene, *cis*-olefin, *trans*-olefin, paraffin. With the eight-membered carbocycles, where the *trans*-olefin is a labile strained modification, the positions of *cis*- and *trans*-cyclooctene respecting refractive index and density are reversed. The nine-membered cyclic hydrocarbons appear to occupy a position intermediate between the eight- and ten-membered series. The refractive indices of *cis*- and *trans*-cyclononene are almost the same. Contrary to the statement of Ziegler and Wilms,<sup>7</sup> the *trans*-olefin is somewhat strained; indicated by its reactivity toward phenyl azide and its thermal isomerization to the *cis* form. The degree of strain is probably not as great as in *trans*-cyclooctene for it is formed, together with the *cis* isomer, in the dehydration of cyclononanol.

The spatial configuration of X is also of interest. An examination of models of this hydrocarbon shows that it is asymmetric and hence it should exist in two enantiomorphic modifications (Fig. 1). There appears to be sufficient restriction in rotation about carbon-carbon bonds to prevent a ready interconversion of the enantiomorphs. In order to confirm isomerism of this type, a study of *trans*-1-cyclononene-6-one, which should be asymmetric and resolvable, is in progress.

The properties of cyclooctyne, as reported by Domin,<sup>8</sup> when compared with similar properties of other eight-membered cyclic hydrocarbons and with the nine- and ten-membered cyclic acetylenes seem to be abnormal. The synthesis and properties of this hydrocarbon are being re-examined.

In order to make the infrared data on the nine-membered hydrocarbons more complete the spectrum for cyclononane is given (Fig. 2). The properties of this specimen of cyclononane were in good agreement with those reported previously.

#### Experimental Part<sup>9</sup>

**Azeloins (2-Hydroxycyclononane) (I).**—This cyclic acyloin was obtained in 35–40% yield from dimethyl azelate following the procedure described for sebacoin.<sup>1</sup> Preparations were carried out on a 2-molar scale and the product used in subsequent reactions showed b.p. 91–103° (3 mm.), with the main portion distilling at 97–100° (3 mm.).

**Cyclononane (II).**—The reduction of I to II was carried out as previously described.<sup>1</sup> I was obtained as its crude semicarbazone, m.p. 150–160°, in 57% yield. After recrystallization from 90% methanol the m.p. was raised to 179.5–180.5°.

Regeneration of II from its semicarbazone was done by steam distilling a mixture of 13.1 g. of II semicarbazone, 22 g. of phthalic anhydride and 45 ml. of water. After collecting 300 ml. of distillate the latter was extracted with ether. From the dried ether extracts there was obtained 8.36 g. (90%) of II: b.p. 100–101.5° (15 mm.);  $n_D^{20}$  1.4768.

The oxime of II was obtained by a standard procedure. From 20 g. of II there was obtained 21.5 g. of crude oxime, m.p. 75–77°. After one recrystallization the oxime (16 g., 74%) showed m.p. 76.5–77.5°.<sup>10</sup>

**1-Chlorocyclononene (III).**—To a suspension of 25 g. (0.12 mole) of phosphorus pentachloride in 50 ml. of benzene there was added with cooling 7 g. (0.05 mole) of II.

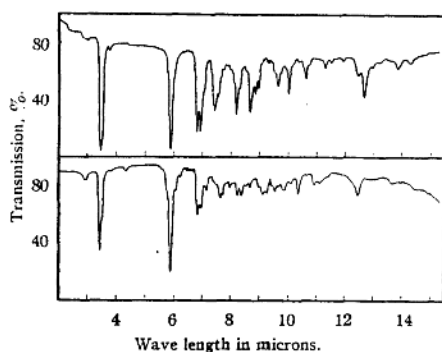


Fig. 4.—Infrared spectra: upper curve, cyclononane; lower curve, 1,2-cyclononanedione.

The mixture was allowed to stand overnight and then worked up in the usual way to remove inorganic compounds. On distillation there was obtained 6.3 g. of a fraction showing b.p. 90–120° (15 mm.) which was largely a mixture of III and 1,1-dichlorocyclononane. This mixture of chloro compounds (6.3 g.) was refluxed for 6 hours with 20 ml. of 20% alcoholic potassium hydroxide. After distilling about 15 ml. of alcohol from the mixture, it was filtered and the filter cake washed with ether. The combined filtrate and ether washings were washed with 30–40% calcium chloride solution, dilute hydrochloric acid and finally with water. Distillation of the dried ether solution gave 2.6 g. (32%) of a pale yellow liquid; b.p. 125–142° (100 mm.). Redistillation of this liquid gave a sample which still possessed a pale yellow color; b.p. 142–144° (100 mm.);  $n_D^{20}$  1.4987;  $d_4^{20}$  1.004.

**Anal.** Calcd. for  $C_9H_{14}Cl$ : C, 68.12; H, 9.51. Found: C, 68.11, 68.16; H, 9.54, 9.58.

**Dehydrohalogenation of III.**—To a distilling flask containing 30 g. (0.65 mole) of potassium hydroxide and 18 ml. of ethanol heated to 125° there was added 14 g. (0.09 mole) of III. Nothing distilled during the addition so the temperature of the mixture was increased gradually to 330°. The cloudy distillate was taken up in 100 ml. of ether and this ether solution washed and dried. After removal of the ether the residue was distilled twice under reduced pressure. Finally there was obtained 1 g. of a colorless liquid which gave a negative Beilstein test for halogen and decolorized potassium permanganate solution and a solution of bromine in carbon tetrachloride: b.p. 105–115° (100 mm.);  $n_D^{20}$  1.4950;  $d_4^{20}$  0.926.

**Anal.** Calcd. for  $C_9H_{14}$ : C, 88.45; H, 11.55. Found: C, 88.30, 88.31; H, 11.60, 11.49.

Quantitative reduction in acetic acid using Adams catalyst required 100.6% of two molar equivalents of hydrogen.

Ozonolysis of the hydrocarbon in ethyl acetate was carried out as previously described.<sup>1</sup> Two solid acidic fractions were obtained: fraction I (less soluble in acetic acid and in water) showed m.p. 129.5–130.5°; fraction II (more soluble in acetic acid and water) showed m.p. 101.0–102.5°. Determination of the m.p. of mixtures of fractions I and II with pimelic, suberic and azelaic acids indicated that fraction I was probably suberic acid. A mixed m.p. of fraction I with an authentic specimen of suberic acid, m.p. 135.6–137.1°, showed 133–136°. The bis-*p*-bromophenacyl ester of fraction I, m.p. 142.8–146.3°, showed m.p. 142.0–143.5°, when mixed with a sample of bis-*p*-bromophenacyl suberate, m.p. 143.9–144.4°. The m.p.'s of mixtures of fraction II with pimelic and azelaic acids did not permit a decision to be made regarding the identity of fraction II. The bis-anilide of fraction II, m.p. 189–190° (micro m.p.), and the bis-*p*-toluidide, m.p. 196–199.5°, demonstrated that II was azelaic acid. This was confirmed by determining the m.p.'s of mixtures of the two derivatives of II with corresponding derivatives of pimelic, suberic and azelaic acids. Approximately equal amounts of fractions I and II were obtained.

(8) N. A. Domin, *J. Gen. Chem. (U. S. S. R.)*, **8**, 851 (1938); *C. A.*, **33**, 1282 (1939).

(9) Melting points are corrected and boiling points are uncorrected except where indicated. The infrared spectra were determined with a Perkin-Elmer Double Beam Infrared Spectrophotometer, Model 21, using a sodium chloride prism. Pure liquid samples, i.e., free of solvents, of varying thickness (up to 0.002 in.) were used in the determinations.

(10) I. Ruzicka, M. Kobelt, O. Häfner and V. Prelog, *Helv. Chim. Acta*, **32**, 544 (1949), report m.p. 79°.

**1,2-Cyclononanedione (VI).**—This  $\alpha$ -diketone was obtained by the oxidation of I using three different reagents. Oxidation of 217 g. of I with 89.3 g. of chromium trioxide in 1000 ml. of glacial acetic acid as described by Prelog, *et al.*,<sup>11</sup> gave 70 g. (33%) of VI; b.p. 80–85° (3 mm.),  $n_D^{20}$  1.4750. Oxidation of 31 g. of I with 102.5 g. of cupric sulfate dissolved in 100 g. of pyridine and 40 g. of water<sup>12</sup> gave 17 g. (55%) of VI; b.p. 80–82° (3 mm.). Finally, oxidation of 39 g. of I in 20 ml. of methanol using 90 g. of copper acetate dissolved in 200 ml. of 50% acetic acid<sup>13</sup> gave 25–28 g. (67–72%) of VI; b.p. 80–82° (3 mm.),  $n_D^{20}$  1.4750.

The dihydrazone of VI was prepared following the procedure described for sebacyl dihydrazone.<sup>1</sup> From 67.8 g. of diketone there was obtained 64–69 g. (80–84%) of VII; m.p. 104–105° (dec.). On recrystallization from commercial absolute ethanol, keeping the temperature below 60°, there was obtained 51.5 g. (84.5%) of VII; m.p. 106–107° (dec.).

*Anal.* Calcd. for  $C_9H_{14}N_4$ : C, 59.30; H, 9.95; N, 30.74. Found: C, 59.24, 59.27; H, 9.85, 10.05; N, 30.34.

**Cyclononyne (IV).**—The procedure used was a modification of the methods previously described.<sup>14</sup> From 52 g. (0.285 mole) of VII there was obtained 15.2 g. (44%) of crude IV on distillation *in vacuo*. Redistillation gave 14 g. (39%) of IV which was still impure; b.p. 67–69° (15 mm.). This impure acetylene was chromatographed through silica gel until fractions of constant refractive index were obtained. The sample of IV thus obtained showed the following properties: b.p. 177–178° (740 mm.) (micro method),  $n_D^{20}$  1.4890,  $d_4^{20}$  0.8972.<sup>14</sup>

*Anal.* Calcd. for  $C_9H_{14}$ : C, 88.45; H, 11.55. Found: C, 88.40, 88.32; H, 11.62, 11.40.

The infrared spectrum for IV was given previously.<sup>1</sup>

Quantitative reduction in acetic acid using Adams catalyst required 102% of two molar equivalents of hydrogen. Ozonolysis of 0.9 g. of IV following the procedure used for cyclodecynyl<sup>1</sup> gave 0.75 g. of an acidic product, m.p. 101–104°. Upon recrystallization from water the product melted at 102–104°. A mixed m.p. with an authentic specimen of azelaic acid was 103–105°. The bis-*p*-toluidide of the acid was prepared and it proved to be identical with the bis-*p*-toluidide of azelaic acid; m.p. 200–200.5°.

Following the procedure described by Thomas, Campbell and Hennion<sup>15</sup> 0.8 g. of IV was hydrated by treatment with a mixture of 80% acetic acid, sulfuric acid and mercuric sulfate. The resulting crude hydration product was converted to a semicarbazone (m.p. 177–179°) which after recrystallization melted at 180–181°. When this semicarbazone was mixed with an authentic specimen of II semicarbazone the m.p. was not depressed.

**Cyclononylamine.**—The oxime of II was reduced to cyclononylamine by means of sodium and absolute ethanol according to methods previously described.<sup>16,17</sup> From 10.2 g. of the oxime there was obtained 7.5 g. (79%) of the amine; b.p. 99–96.5° (12 mm.),  $n_D^{20}$  1.4851.

**Cyclononyltrimethylammonium Iodide (VIII).**—Using a procedure described by Ziegler and Wilms,<sup>18</sup> 8.6 g. of cyclononylamine was converted to the quaternary salt VIII. After recrystallization from water there was obtained 17 g. (90%) of crystalline VIII; m.p., on the Dennis bar, 273–273.5° (dec.) (uncor.).

*Anal.* Calcd. for  $C_9H_{14}I$ : C, 46.29; H, 8.43. Found: C, 46.32, 46.23; H, 8.38, 8.45.

**trans-Cyclononyne (X).** A. From VIII.—A solution of 16 g. of VIII in 100 ml. of water was treated with an excess of freshly precipitated silver oxide. After filtering, the filtrate gave a negative test for silver and iodine ions. This filtrate was concentrated and decomposed at 140–160° at the water-

pump. The distillate was extracted with ether and the ether extracts washed and dried. On distillation there was obtained 4.4 g. (69%) of X; b.p. 73–74° (30 mm.);  $n_D^{20}$  1.4798. The hydrocarbon was then chromatographed through silica gel giving a series of fractions having practically the same refractive index:  $n_D^{20}$  1.4799;  $d_4^{20}$  0.8615.

*Anal.* Calcd. for  $C_9H_{16}$ : C, 87.02; H, 12.98. Found: C, 87.09, 87.20; H, 12.93, 13.11.

The infrared spectrum of this sample of X (Fig. 2) showed a very strong absorption at 10.25  $\mu$ .

Quantitative reduction in acetic acid using Adams catalyst required 100.5% of one molar equivalent of hydrogen.

On ozonolysis only azelaic acid was obtained (86%). The acid was characterized by methods previously described under the ozonolysis of IV.

Treatment of this sample of X (0.5 ml.) with 0.6 ml. of phenyl azide according to the procedure of Ziegler and Wilms<sup>18</sup> gave a crystalline solid within a few hours. Heat was evolved on mixing the two compounds and the mixture solidified after standing at room temperature for 2 hours and cooling in the refrigerator 30 minutes. The phenyl azide adduct was recrystallized from petroleum ether; m.p. 97.3–98.2°.

*Anal.* Calcd. for  $C_{10}H_{18}N_2$ : C, 74.03; H, 8.70; N, 17.27. Found: C, 73.60; H, 8.66; N, 17.17.

B. From IV.<sup>14</sup>—To a solution of 1.38 g. (0.06 g. atom) of sodium in 60 ml. of purified liquid ammonia<sup>19</sup> there was added dropwise with stirring 2.44 g. (0.02 mole) of IV ( $n_D^{20}$  1.4890). After stirring for 2 hours excess sodium was decomposed by adding ammonium nitrate to the disappearance of the blue color. Dilute aqueous ammonia (50 ml.) was then carefully added. The reaction mixture was extracted with benzene, the benzene extracts washed with dilute hydrochloric acid, sodium bicarbonate solution, water and dried. After removal of the benzene there was obtained 1.83 g. of a colorless liquid; b.p. 73–74° (30 mm.). This distillate was chromatographed through silica gel and 86% of the material obtained showed  $n_D^{20}$  1.4800. The remaining 14% was identified through its refractive index and infrared absorption as unreduced IV. The infrared curve (Fig. 2) of this reduction product indicated it to be X.

This sample of X formed an adduct with phenyl azide just as rapidly as did the sample described under A; m.p. 97–97.3°. A m.p. determination of a mixture of the two phenyl azide adducts showed no depression.

**cis-Cyclononyne (XI).** From IV.<sup>20</sup>—Using the procedure described for the selective catalytic hydrogenation of cyclodecynyl<sup>1</sup> 3.04 g. of IV in 4 ml. of ethyl acetate gave, after two distillations, 2.47 g. (81%) of XI; b.p. 167–169° (740 mm.). When chromatographed through silica gel all fractions showed the same refractive index;  $n_D^{20}$  1.4805,  $d_4^{20}$  0.8671.

The infrared spectrum of this sample of XI (Fig. 3) showed general absorption in the region 13.5–14.5  $\mu$  and no absorption at 10.25  $\mu$ .

*Anal.* Calcd. for  $C_9H_{16}$ : C, 87.02; H, 12.98. Found: C, 86.99, 87.03; H, 12.89, 12.90.

Quantitative reduction in acetic acid using Adams catalyst required 101% of one molar equivalent of hydrogen.

On ozonolysis only azelaic acid was obtained (70% as pure acid). The azelaic acid was characterized as previously described under IV.

On treating 0.5 ml. of XI with 0.6 ml. of phenyl azide there was no observable heat of reaction. After the mixture had stood in the refrigerator for 4 weeks there was no separation of a crystalline product.

**Isomerization of X.**—Following the procedure of Ziegler and Wilms<sup>18</sup> a mixture of 0.93 g. of X ( $n_D^{20}$  1.4800), 0.018 g. of hydroquinone and 0.018 g. of  $\beta$ -naphthalenesulfonic acid was heated at 150° under nitrogen in a sealed tube for 1.5 hours. After filtering, taking up in benzene, washing the benzene solution and drying there was obtained on distilla-

(11) V. Prelog, L. Frankel, M. Koeblt and P. Barman, *Helv. Chim. Acta*, **30**, 1741 (1947).

(12) H. Gilman and A. H. Blatt, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 87.

(13) P. Ruggli and P. Zeller, *Helv. Chim. Acta*, **28**, 741 (1945).

(14) The value  $d_4^{20}$ , 0.8979 was reported previously. The present figure is considered to be more nearly correct.

(15) R. J. Thomas, K. N. Campbell and C. F. Hennion, *THIS JOURNAL*, **60**, 718 (1938).

(16) A. H. Blatt, "Organic Syntheses," Col. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 313.

(17) V. Prelog, M. F. El-Newehy and O. Hädiger, *Helv. Chim. Acta*, **33**, 305 (1950).

(18) (a) A. I. Henne and K. W. Greenlee, *THIS JOURNAL*, **68**, 2020 (1943); (b) K. N. Campbell and L. T. Eby, *ibid.*, **63**, 216 (1941); (c) M. C. Hoff, K. W. Greenlee and C. E. Boord, *ibid.*, **73**, 3329 (1951).

(19) The liquid ammonia was purified by adding a small amount of sodium and then distilling the ammonia directly into a well dried reaction vessel.

(20) (a) M. L. Sherrill and E. S. Matlack, *THIS JOURNAL*, **59**, 2124 (1937); (b) P. Pignatelli, "Acetylene Homologs and Derivatives," Mapleton House, Brooklyn, N. Y., 1950, p. 128.

tion ca. 0.5 g. of a colorless liquid; b.p.  $70^{\circ}$  (28 mm.),  $n_D^{20}$  1.4801.

*Anal.* Calcd. for  $C_9H_{16}$ : C, 87.02; H, 12.98. Found: C, 87.18; H, 12.82.

The infrared spectrum of this product (Fig. 3) showed strong absorption in the region 13.5–14.5  $\mu$  and no absorption at 10.25  $\mu$  indicating the substance to be XI.

This sample of XI when mixed with phenyl azide showed no observable reaction over a period of 2 weeks.

**Cyclononanol (IX).**—The reduction of 32.6 g. (0.023 mole) of II with lithium aluminum hydride gave 31 g. (94%) of distilled cyclononanol; b.p. 115–119 $^{\circ}$  (15 mm.),  $n_D^{20}$  1.4903.

**Dehydration of IX.**—Following a procedure previously described for the dehydration of cyclodecanol<sup>1</sup> 13.1 g. (0.09 mole) of IX was added to 45 g. of boiling phthalic anhydride. Distillation of the reaction product gave 8 g. of a colorless liquid; b.p. 51.3–53 $^{\circ}$  (7 mm.),  $n_D^{20}$  1.4776. This

distillate was then chromatographed through silica gel. About 60% of the fractions thus obtained showed  $n_D^{20}$  1.4792–1.4796. The infrared spectrum of this material (Fig. 3) showed characteristic absorption for both X and XI.

*Anal.* Calcd. for  $C_9H_{16}$ : C, 87.02; H, 12.98. Found: C, 87.05, 87.15; H, 12.53, 12.98.

Quantitative reduction of this mixture of cyclononenes in acetic acid using Adams catalyst required 98.91% of one molar equivalent of hydrogen.

**Cyclononane.**—The products obtained in the quantitative hydrogenation of the various samples of cyclononene were combined and distilled. The sample of cyclononane thus obtained showed b.p. 171–172.5 $^{\circ}$  (740 mm.) (lit. gives b.p. 170–172 $^{\circ}$  (760 mm.))<sup>21</sup> and  $n_D^{20}$  1.4663. The infrared spectrum of this sample of cyclononane is shown in Fig. 2.

(21) N. D. Zelinsky, *Ber.*, **40**, 3277 (1907).

ITHACA, N. Y.

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

## Many-membered Carbon Rings. VII. Cyclooctyne

BY A. T. BLUMQUIST<sup>1</sup> AND LIANG HUANG LIU<sup>2</sup>

RECEIVED DECEMBER 29, 1952

Cyclooctyne has been obtained by the alkali-catalyzed oxidative decomposition of 1,2-cyclooctanedione dihydrazone. Its structure is indicated by its infrared absorption spectrum and by chemical behavior upon ozonolysis, catalytic reduction and hydration.

Recently it was shown that the application of classical methods to the synthesis of simple cyclic acetylenes in the intermediate carbocyclic range, cyclononyne<sup>1</sup> and cyclodecyne,<sup>2</sup> failed to give pure acetylene free of other unsaturated compounds. This observation prompted a study of cyclooctyne whose synthesis from 1-bromo-2-chlorocyclooctene was reported by Domnin.<sup>4</sup> That Domnin had at hand pure cyclooctyne is doubtful. It has been shown that his method of synthesis produces a mixture of allene and acetylene when applied to the C<sub>10</sub>-carbocycle. The refractive index and density of his hydrocarbon are inconsistent with the values for such properties reported for the very closely related simple cyclic acetylenes, olefins and paraffins.<sup>1,3,5</sup> Finally, the chemical evidence in support of the cyclooctyne structure for his hydrocarbon is insufficient. In fact, all of the properties of Domnin's cyclooctyne may be accounted for better on the assumption that the hydrocarbon was a mixture of cyclooctene and cyclooctane.

Cyclooctyne, free from the isomeric 1,2-cyclooctadiene and other unsaturated hydrocarbons, has been obtained by the alkali-catalyzed oxidative decomposition of 1,2-cyclooctanedione dihydrazone. Purification of the hydrocarbon, achieved by distillation and chromatographic adsorption, was followed by refractive index and infrared spectrum measurements.

The infrared spectrum of cyclooctyne having  $n_D^{20}$  1.4850 and  $d_4^{20}$  0.868 was determined. Characteristic absorption at 4.53  $\mu$  ( $\text{C}\equiv\text{C}$  stretching) was observed similar to that found for cyclononyne and cyclodecyne.<sup>6</sup> This sample of cyclooctyne absorbed 102% of two molar equivalents of hydrogen upon quantitative reduction and gave only suberic acid upon ozonolysis. Upon hydration it was converted to cyclooctanone, characterized as its semicarbazone.

That cyclooctyne is probably highly strained was indicated by its explosive reaction with phenyl azide.

The cyclic intermediates suberoin and suberil required for the synthesis have not been previously described.<sup>6a</sup> They were obtained by modification of methods previously described for similar derivatives of the C<sub>9</sub>- and C<sub>10</sub>-carbocycles.<sup>1,3</sup> Their infra-

red spectra were determined and they corresponded closely to those of the related C<sub>9</sub>- and C<sub>10</sub>-homologs.<sup>1,3</sup>

The preparation of suberoin by the acyloin condensation of diethyl suberate proved to be particularly troublesome when carried out following the procedure used for azeloin and sebacin.<sup>1,3</sup> During the condensation the reaction mixture became so gelatinous that it was impossible to maintain effective stirring and the tendency for charring to occur became quite marked. By carrying out the condensation in a refluxing mixture of toluene and xylene and by careful control of the rate of addition these difficulties were eliminated and suberoin was obtained in satisfactory yield.

Suberoin was characterized as its semicarbazone and *p*-phenylazobenzoate while suberil was converted to its quinoxaline derivative, its dihydrazone, and oxidized to suberic acid using periodic acid.

The isolation of cyclooctyne free from oxygen containing compounds required careful exclusion of air as the acetylene was very prone to react with oxygen. Also in the course of isolating the acetylene certain observations indicated that there was a tendency for cyclooctyne to rearrange to a more stable isomeric hydrocarbon showing less unsaturation. This may possibly be the bicyclooctene I.



Further studies related to these observations are in progress.

### Experimental Part<sup>7</sup>

**Suberoin (2-Hydroxycyclooctanone).**—The procedure previously described for the preparation of sebacin<sup>3</sup> was modified in order to avoid the formation of a thick gelatinous reaction mixture which could be stirred only with extreme difficulty and which readily charred when heated. The use of a mixture of toluene and xylene as a reaction solvent eliminated these difficulties. For 115 g. (0.5 mole) of pure diethyl suberate a mixture of 1190 ml. of xylene and 310 ml. of toluene was used as the solvent. The ester was added carefully over a six-hour period. Decomposition of the reaction mixture was carried out with 50 ml. of methanol followed by 240 ml. of 50% aqueous acetic acid. From ten preparations a suberoin fraction showing b.p. 70–81° (2 mm.) was obtained in 50–56% yield. After two redistillations, suberoin showing b.p. 75° (1.5 mm.) and m.p. 33–37° was obtained in 35% yield.<sup>7a</sup>

(7) Melting points are corrected and boiling points are uncorrected except where indicated. The infrared spectra were determined with a Perkin-Elmer double beam infrared spectrophotometer, model 21, using a sodium chloride prism. Pure liquid samples of varying thickness were used in the determinations.

(7a) The discrepancy in m.p. of our suberoin (33–37°) with that reported by Cope (37–38.5°), see ref. 6a, is very likely due to the presence of some suberoin dimer in our suberoin. The tendency for cyclic acyloins to dimerize has been demonstrated by J. C. Sheehan, R. C. O'Neil and M. A. White, *This Journal*, 72, 3376 (1950).

(1) For the preceding paper in this series see A. T. Blumquist, L. H. Liu and J. C. Bohrer, *This Journal*, 74, 3643 (1952).

(2) Postdoctoral Research Fellow under the du Pont grant-in-aid, 1951–1952.

(3) A. T. Blumquist, R. E. Burge, Jr., and A. C. Suesy, *This Journal*, 74, 3636 (1952).

(4) N. A. Domnin, *J. Gen. Chem. (U.S.S.R.)*, 3, 351 (1953); *C. A.*, 48, 1282 (1953).

(5) K. Ziegler and H. Wilms, *Ann.*, 567, 1 (1950).

(6) A. T. Blumquist, *et al.*, *This Journal*, 73, 5510 (1951).

(6a) The preparation of suberoin from dimethyl suberate was recently described by Cope and co-workers; *ibid.*, 74, 3884 (1952).



The infrared spectrum of suberoin was similar to that of sebacoin<sup>8</sup> showing strong absorption at 2.92 and 5.90  $\mu$ , OH and CO stretching, respectively.

*Anal.* Calcd. for  $C_{18}H_{30}O_4$ : C, 67.57; H, 9.92. Found: C, 67.55, 67.39; H, 9.88, 10.01.

Suberoin semicarbazone, m.p. 179.5–180°, was obtained in 70% yield after two recrystallizations from ethanol.

*Anal.* Calcd. for  $C_{18}H_{28}O_2N_2$ : C, 54.25; H, 8.80; N, 21.09. Found: C, 54.23, 54.50; H, 8.53, 8.82; N, 21.02, 21.06.

Suberoin *p*-phenylazobenzoate after purification by chromatographing and recrystallizing showed m.p. 128.5–129°.

*Anal.* Calcd. for  $C_{24}H_{30}O_4N_2$ : C, 71.99; H, 6.33; N, 7.99. Found: C, 72.01, 72.03; H, 6.36, 6.40; N, 8.08, 8.10.

Suberil (1,2-Cyclooctanedione).—This  $\alpha$ -diketone was obtained in approximately the same yield by the oxidation of suberoin using either of two reagents. Oxidation of 21.3 g. (0.15 mole) of suberoin using 60 g. (0.30 mole) of cupric acetate monohydrate in 10 ml. of methanol and 150 ml. of 50% acetic acid<sup>9</sup> gave 64–70% of crude suberil showing b.p. 65.5–77° (3 mm.). Oxidation of 21.3 g. (0.15 mole) of suberoin using 28 g. (0.06 mole) of bismuth oxide in 75 ml. of acetic acid<sup>9</sup> gave a 62% yield of suberil. Upon redistillation the pure diketone showed b.p. 68.8–69.5° (3 mm.). Freezing point determinations of the solid diketone after four redistillations were unsatisfactory.

The infrared spectrum of suberil was similar to those of sebacil<sup>1</sup> and 1,2-cyclononanedione<sup>3</sup> showing very strong absorption at 5.88  $\mu$ , CO stretching, and weak absorption at 2.90–2.98  $\mu$ , OH stretching.

*Anal.* Calcd. for  $C_8H_{12}O_2$ : C, 68.54; H, 8.63. Found: C, 68.65, 68.85; H, 8.65, 8.78.

The quinoxaline derivative of suberil was prepared by the method of Leonard and Mader.<sup>10</sup> It was obtained in 75% yield after recrystallizations from ethanol; m.p. 120.2–120.7°.

*Anal.* Calcd. for  $C_{14}H_{12}N_2$ : C, 79.20; H, 7.60; N, 13.20. Found: C, 79.06, 79.00; H, 7.62, 7.60; N, 13.20.

(8) P. Ruggli and P. Zeller, *Helv. Chim. Acta*, **28**, 741 (1945).

(9) W. Rigby, *J. Chem. Soc.*, 793 (1931).

(10) N. J. Leonard and P. M. Mader, *THIS JOURNAL*, **72**, 5388 (1950).

Oxidation of suberil with periodic acid afforded suberic acid, m.p. 140–141°, in 59% yield. A mixed m.p. determination with an authentic specimen of suberic acid showed no depression.

The dihydrazone of suberil was prepared following the method described for sebacil dihydrazone.<sup>1</sup> The crude dihydrazone, m.p. 103–104.5°, was obtained in 93% yield. Careful recrystallization from benzene, keeping the temperature below 60°, gave the pure hydrazone (69%), m.p. 105–106°.

*Anal.* Calcd. for  $C_8H_{12}N_4$ : C, 57.11; H, 9.59; N, 33.30. Found: C, 57.40, 57.12; H, 9.46, 9.58; N, 33.00.

Cyclooctyne.—The preparation and purification procedures were similar to those for cyclononyne<sup>1</sup> with the following modifications. The reaction mixture was heated at 80° with a water-bath, length of heating was reduced to 5–8 hr. depending upon cessation of evolution of nitrogen, and all distillations were carried out under nitrogen.

The impure distilled acetylene was obtained in 9.3% yield. After purification by chromatographing, the pure acetylene showed b.p. 157.5–158° (740 mm.) (micro method),  $n_D^{20}$  1.4850 and  $d_4^{20}$  0.868 (micro method).

The infrared spectrum of cyclooctyne was similar to those of cyclononyne and cyclodecyne<sup>1</sup> showing weak absorption at 4.53  $\mu$  characteristic of  $C\equiv C$  stretching.

*Anal.* Calcd. for  $C_8H_6$ : C, 88.82; H, 11.18. Found: C, 88.83, 89.00; H, 10.93, 11.09.

Quantitative reduction in acetic acid using Adams catalyst required 102% of two molar equivalents of hydrogen.

Ozonolysis of 0.4 g. of cyclooctyne following the procedure used for cyclononyne<sup>1</sup> gave 0.43 g. of an acidic product which showed a m.p. of 138.5–140° after two recrystallizations. When this acidic product was mixed with an authentic specimen of suberic acid the m.p. was not depressed.

Hydration of 0.2 g. of cyclooctyne using the procedure described for cyclononyne<sup>1</sup> gave 0.2 g. of an oil of camphor-like odor. This oil was converted to a semicarbazone having m.p. 170–171°. The m.p. of a mixture of this semicarbazone and authentic cyclooctanone semicarbazone was not depressed.

When treated with phenyl azide, according to the procedure of Ziegler and Wilms,<sup>1</sup> cyclooctyne reacted explosively forming a viscous liquid product which was not characterized.

ITHACA, N. Y.