THE SYNTHESIS OF A WATER-SOLUBLE MOLECULE

CONTAINING A HYDROPHOBIC CAVITY

by

W. HARRY MANDEVILLE

B. S. Colorado School of Mines

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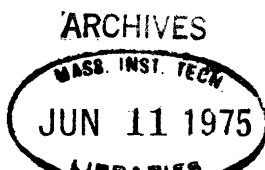
May 16, 1975

Signature of Author _____
                                      Department of Chemistry
                                              May   , 1975

Certified by _____
                                              Thesis Supervisor

Accepted by _____
                                      Chairman, Departmental
                                                  Committee

This Doctoral Thesis has been examined by a committee of the Department of Chemistry as follows:

Professor Dietmar Seyferth _____

                                                    Chairman

Professor George M. Whitesides _____

                                                    Thesis Supervisor

Professor K. Barry Sharpless

to SUSIE...

143

for CHRISTMAS and SNOW

and

to MY PARENTS

"You know how when you stand
in the rain with your mouth open
how rarely the raindrops hit your
tongue... Chemistry is a lot like
that. I like standing in the rain."

April 30, 1975

THE SYNTHESIS of a WATER-SOLUBLE MOLECULE
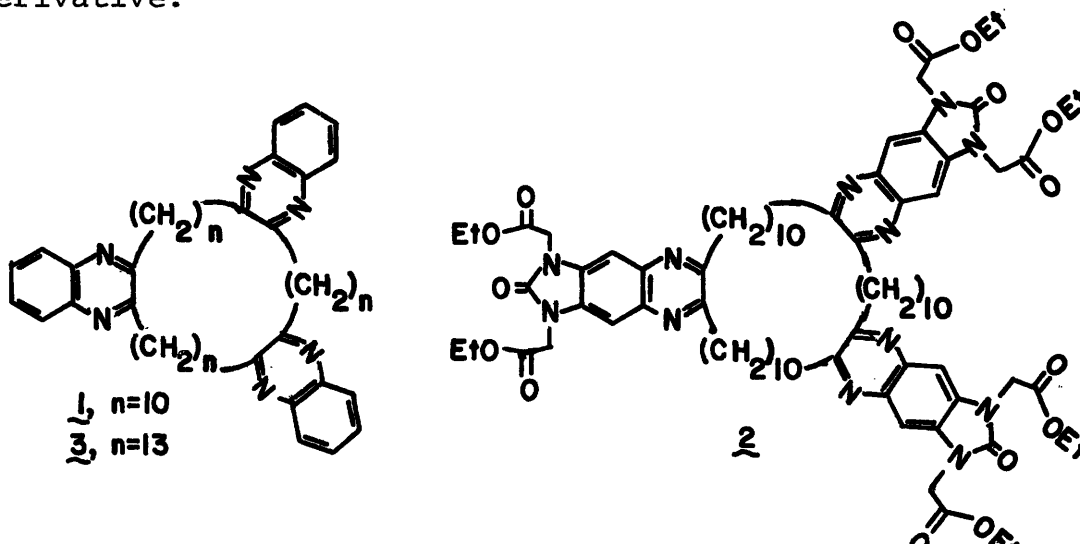
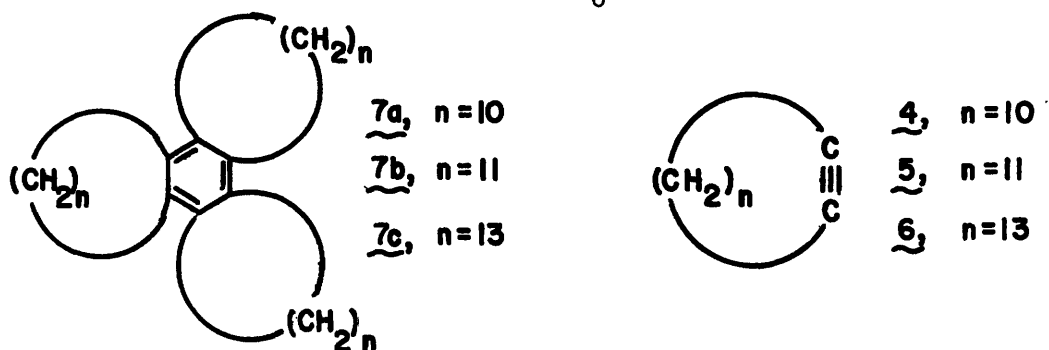## CONTAINING a HYDROPHOBIC CAVITY

by

W. Harry Mandeville

Submitted to the Department of Chemistry at the Massachusetts Institute of Technology, May 16, 1975, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

ABSTRACT

Part I: The Synthesis of a Water-Soluble Molecule Containing a Hydrophobic Cavity

The syntheses and characterization of three macrocyclic compounds, cyclohexatriaconta[1,2,13,14,25,26-b,b',b"]tris-quinoxaline (1) cyclohexatriaconta[1,2,13,14,25,26-b,b',b"]tris(diethyl 1H,3H,2-oxoimadazo[4,5-g]quinoxalino-1,3-di-α-acetate) (2) and cyclopentatetraconta[1,2,16,17,31,32-b,b',b"]trisquinoxaline (3) are described. These compounds have been prepared from the benzene derivatives tris(deca-methylene)benzene (7a) and tris(tridecamethylene)benzene (7c) via a ring-opening ozonolysis. Compounds 7a and 7c were prepared from the corresponding cyclic acetylenes, cyclo-dodecyne (4) and cyclopentadecyne (6) via a titanium trichloride catalyzed cyclotrimerization. A new, convenient synthesis for the cyclic alkynes 4 and 6, utilizing the corresponding cyclic ketones as starting materials, is also described. One other compound, tris(hendecamethylene)benzene (7b) was also prepared but its ozonolysis did not yield the expected macrocyclic derivative.

1, n=10
3, n=13

2

(CH$_2$)$_n$

7a, n=10

7b, n=11

7c, n=13

(CH$_2$)$_n$

(CH$_2$)$_n$

4, n=10

5, n=11

6, n=13

(CH$_2$)$_n$

Part II: The Elucidation of the Mechanism of Oxidation with Adams' Catalyst.

Several mechanisms for the oxidation of alcohols by Adams' catalyst and molecular oxygen are postulated. Each of these mechanisms is discussed with respect to evidence already in the literature and with respect to new evidence found in the present work. The deuterium isotope effect for the oxidation of 2-propanol-d$_1$ has been determined to be 1.8. The competitive oxidation of cis- and trans-4-t-butylcyclohexanol has shown the oxidation follows the same stereochemical path as the von Auwers-Skita rule dictates for the reduction of cyclohexanones with hydrogen. The oxidation of cyclobutanol and cyclopentanol show the reaction does not proceed via a homolytic cleavage of a hydrogen-oxygen bond to form a metal-oxygen bond.

Part III: Selectivity in Organic Group Transfer in Reactions of Mixed Lithium Diorganocuprates.

This work has been published: W. Harry Mandeville and George M. Whitesides, J. Org. Chem., 39, 400 (1974).

Thesis Supervisor: George M. Whitesides
Title: Professor of Chemistry

ACKNOWLEDGEMENTS

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LIST of FIGURES and SCHEMES

Part I.

The Synthesis of a Water-Soluble Molecule

Containing a Hydrophobic Cavity.

Functionalized carbocyclic compounds of ring size

greater than 10 carbon atoms have been the subject of

synthetic efforts for many years. [1]

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1) (a) L. Ruzicka, Helv. Chim. Acta, 9, 715, 1008 (1936);
    (b) K. Ziegler, H. Eberle, H. Olinger, Justus Liebigs
    Ann. Chem., 504, 94 (1933); (c) A. T. Bloomquist,
    R. D. Spencer, J. Am. Chem. Soc., 69, 472 (1947); (d)
    N. J. Leonard, C. W. Schimerphenig, J. Org. Chem., 23,
    1708 (1958); (e) V. Prelog, L. Frenkiel, M. Kobelt,
    O. Barman, Helv. Chim. Acta, 30, 1741 (1947); (f)
    V. Prelog, K. Schenker, H. Gunthard, ibid., 25, 1598
    (1952); (g) M. Stoll, ibid., 30, 1822 (1947); (h)
    G. Schill, K. Rothmaier, H. Ortlieb, Syn., 426 (1973);
    (i) G. Schill, U. Keller, ibid., 621 (1973); (j)
    P. Heimbach, W. Brenner, Angew. Chem., 78, 938 (1966);
    (k) P. Heimbach, W. Brenner, Angew. Chem. Int. Ed. Engl.,
    5, 961 (1966); (l) W. Brenner, P. Heimbach, K. Ploner,
    F. Thomel, Justus Liebigs Ann. Chem., 1882 (1973);
    (m) E. Wasserman, D. A. Ben Efrain, R. Wolovsky,
    J. Am. Chem. Soc., 90, 3286 (1968); (n) G. Natta,
    G. D'allasta, I. W. Bass, G. Carella, Makromol. Chem.,
    91, 87 (1966); (o) K. Wolovsky, Z. Nir, Syn., 124 (1972);
    (p) P. Busch, P. R. Story, ibid., 181 (1970); (q)
    R. J. Kaufman, Ph. D. Thesis, Mass. Inst. of Tech.,
    1974; (r) R. Epsztein, I. Marszak, Compt. rend., 243,
    283 (1956).

So far, no good method has been published for the synthesis

of symmetrically functionalized carbocyclic compounds of ring

size greater than 30.

This thesis describes the synthesis of tris(symmetrically

functionalized) cyclohexatriacontanes and cyclopentatetra-

contanes from readily available starting materials. These

compounds, cyclohexatriaconta[1,2,13,14,25,26-b̲,b̲',b̲"]-

trisquinoxaline (1̲) cyclohexatriaconta[1,2,13,14,25,26-b̲,

b̲',b̲"]tris(diethyl 1H̲,3H̲,2-oxoimidazo[4,5-g̲]quinoxaline-1,3-

di-α-acetate) (2̲) and cyclopentatetraconta[1,2,16,17,31,32-

b̲,b̲',b̲"]trisquinoxaline (3̲) have been prepared from the

corresponding cyclic acetylenes, cyclododecyne (4̲) and cyclo-

pentadecyne (6̲) via a sequence involving a cyclotrimerization
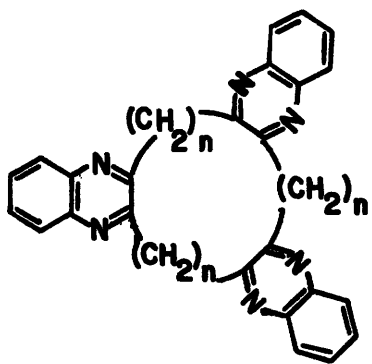
1̲, n = 10
3̲, n = 13
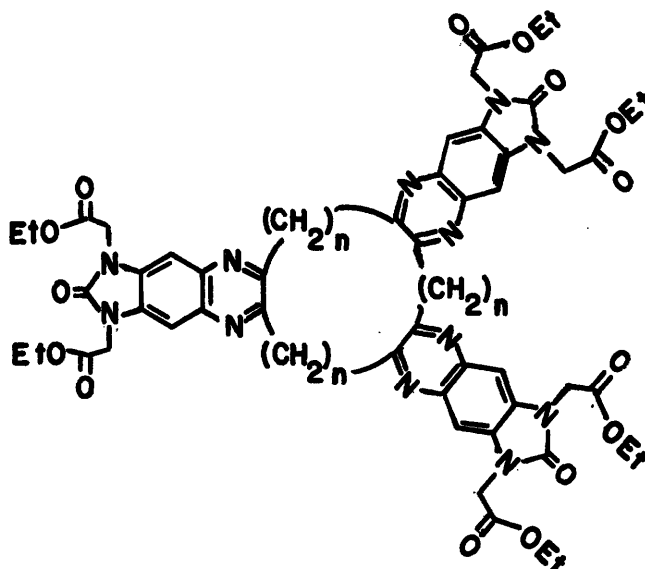
2̲, n = 10

reaction to yield the benzene derivative (7) which is then
ozonolyzed. Preparation of the α-diketone compounds cyclo-
dodecane-1,2-dione (8) and cyclohexatriacontane-1,2,13,14,
25,26-hexone (9) by this route was described briefly by
Regen[2] and extensively studied here; cyclopentadecane-1,2-

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2) S. L. Regen, Ph. D. Thesis, Mass. Inst. of Tech., 1972.

_____

dione (12) and cyclopentatetracontane-1,2,16,17,31,32-
hexone (13) were obtained by related procedures starting
with cyclopentadecyne (6).

Scheme I-1.

4, n = 10
5, n = 11
6, n = 13

7a, n = 10
7b, n = 11
7c, n = 13

9, n = 10
11, n = 11
13, n = 13

8, n = 10
10, n = 11
12, n = 13
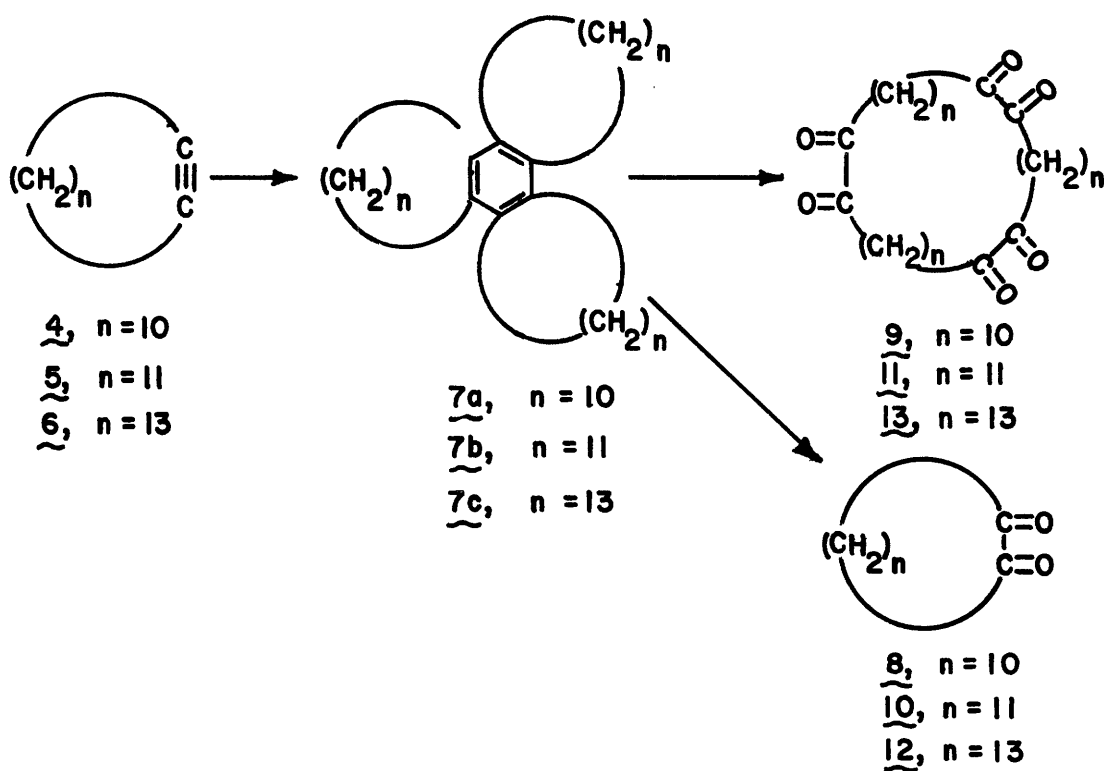
The derivatives 1-3 are then prepared via an unexceptional,
acid-catalyzed condensation with ortho-phenylenediamine (14)
or diethyl-5,6-diaminobenzimidazolone-1,3-diacetate (15).
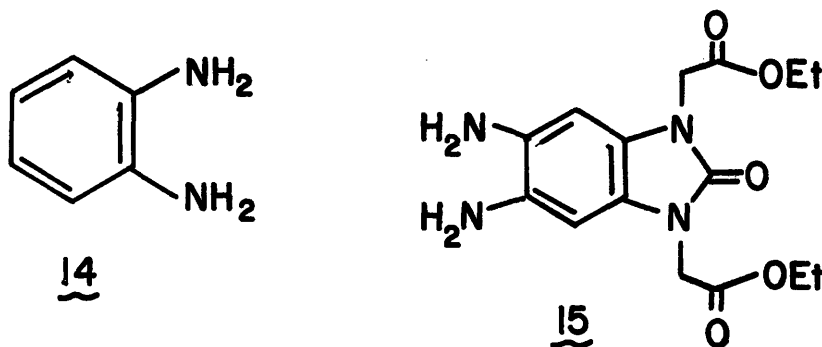
Cyclododecyne, Cyclotridecyne and Cyclopentadecyne.
Cyclic acetylenes have been prepared by several methods.
Meier[3a] and Kolinskii[3b] in recent reviews, describe most of

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3) (a) H. Meier, Syn., 235 (1972); (b) R. Kolinskii,
    Russ. Chem. Rev. (Engl.), 30, 309 (1961).

---

the currently used procedures for synthesizing cyclic
acetylenes in the ring systems containing 6-17 carbon atoms.
Many of the procedures possess synthetic merit but all
suffer from the common maladies of low yield and formation of
unwanted side products. Meier and Menzel[4] describe a synthesis

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4) H. Meier, I. Menzel, Syn., 215 (1971).

---

of cyclic acetylenes from the corresponding cyclic ketones

for the 8-, 12- and 15-carbon ring systems. The reaction

proceeds via a selenium dioxide oxidation to the α-diketone,

preparation of a bistosylhydrazone and subsequent photolysis

to yield the cyclic alkyne. The overall yields are 20, 22

and 23% for the 8-, 12- and 15-carbon rings, respectively.

Nozaki and Noyori[5] describe a synthesis of cyclododecyne

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5) H. Nozaki, R. Noyori, J. Org. Chem., 30, 1652 (1965).

---

from the corresponding cis-olefin by a bromination and

subsequent elimination. The overall yield in this sequence

is 50%, but the procedure is complicated by the fact that

the cis-olefin must first be prepared by diimide reduction

of 1,5,9-trans,trans,cis-cyclododecatriene. Prelog[6] has

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6) (a) V. Prelog, M. Speck, Helv. Chim. Acta, 38, 1786
(1955); (b) V. Prelog, V. Boarland, M. Speck, ibid.,
38, 1776 (1955).

---

obtained cyclohendecyne and cyclododecyne from the corresponding

1,2-diketones by preparation of the 1,2-bishydrazone and

subsequent oxidation with mercuric oxide to give cyclododecyne.

The yield is not given; in our laboratory[2] however, this

reaction gives cyclododecyne in 36% yield from the 1,2-bis-

hydrazone. Sicher et al[7] and Tsuji et al[8] have similarly

7) J. Sicher, M. Svoboda, J. Zavada, Collect. Czech. Chem. Commun., 30, 421 (1965).

8) J. Tsuji, H. Takahashi, T. Kajimoto, Tet. Letters, 4573 (1973).

oxidized 1,2-bishydrazones to obtain cyclic acetylenes in good yield using mercuric oxide and cuprous oxide/air.

In the last two methods, the yields obtained were good, but all of the last three methods require the difficultly prepared α-diketone as starting material.

In light of these difficulties, a new method was developed which easily affords large quantities of cyclododecyne and other cyclic acetylenes. The new procedure involves preparation of the 1,1-dichloride from the cyclic ketone and phosphorous pentachloride.[9] The geminal dichloride

9) M. S. Newman, L. Wood, J. Am. Chem. Soc., 81, 4300 (1959).

when treated with potassium t-butoxide in DMSO yields the equilibrium mixture of cyclic allene and cyclic alkyne. Cyclopentadecyne is prepared from cyclopentadecanone in the same manner.

In a typical experiment, cyclododecanone is converted to 1,1-dichlorocyclododecane in 98% yield in benzene (or methylene chloride) at 0° using a 50% excess of phosphorous

pentachloride. The cyclic dichloride is then added to 3.3
equivalents of potassium t-butoxide in DMSO and stirred
overnight at room temperature. Distillation after work-up
yields the equilibrium mixture of cyclododecyne and cyclo-
dodeca-1,2-diene in 81% overall yield from cyclododecanone.
In this case, the equilibrium mixture consists of 74% alkyne
and 26% allene. Cyclopentadecyne was prepared from cyclo-
pentadecanone via an identical procedure to give the cycloalkyne
in 79% yield. The equilibrium for this system lies wholly
on the side of the cyclic alkyne; no cyclopentadeca-1,2-diene
is formed in the reaction.

The reaction probably proceeds through an initial
elimination to yield a mixture of the cis and trans-vinyl
chlorides. These are the observed products when KOH is used
as the base in ethanol. The mixture of vinyl chlorides will
eliminate once more under the conditions employed but the
product analysis becomes more complex. The trans-vinyl
chloride can eliminate to yield either the cyclic acetylene or
the cyclic allene, but the cis-vinyl chloride yields only the
cyclic allene on subsequent elimination. The possibility also
exists for isomerization of the cis-vinyl chloride to the trans-
olefin followed by elimination to yield the cyclic alkyne.[10]

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10) J. Klein, E. Gurfinkle, Tetrahedron, 26, 2127 (1970).

Potassium t-butoxide in DMSO is known to equilibrate cyclic

allene/alkyne mixtures[11] and therefore the resulting product

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11) (a) H. E. Viehe, "Chemistry of Acetylenes", H. E. Viehe, Ed., Marcel Dekker, New York, N. Y., 1969, p. 1031; (b) L. Brandsma, "Preparative Acetylene Chemistry," Elsevier, New York, N. Y., 1971, p. 143; (c) H. Nozaki, S. Kato, R. Noyori, Can. J. Chem., 44, 1021 (1966).

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is only the equilibrium mixture of cyclic acetylene and

cyclic allene. The elimination process is outlined in

Scheme I-2.

Scheme I-2.
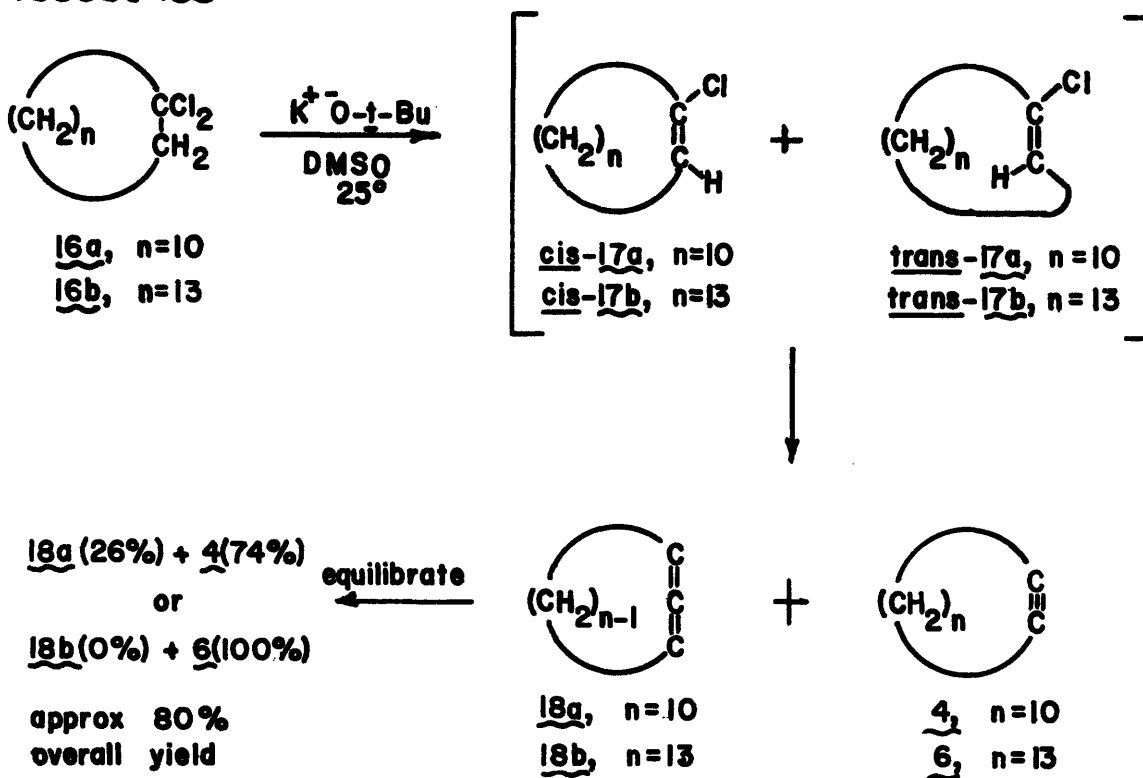
The equilibrium ratios of cyclic acetylene to cyclic allene have been determined for the series of cycloalkynes of ring size 8-11[11a] and for the cyclotridecyne system.[11c]

Cyclotridecyne, 5, was not prepared in the preceding manner but was instead prepared as described by Nozaki, Kato and Noyori.[11c] This route involved addition of dibromocarbene to cyclododecene followed by methyllithium metal-halogen exchange and spontaneous ring opening of the resulting cyclopropylcarbene to yield cyclotrideca-1,2-diene. The cycloallene was then isomerized to the cyclic alkyne with potassium t-butoxide in DMSO. The commercial mixture (Chemical Samples Co.) of cis- and trans-cyclododecene was used in this preparation rather than the pure cis-isomer as described by these authors.

The synthesis of cyclododecyne and cyclopentadecyne from the corresponding cyclic ketones represents an extremely useful route for the preparation of cyclic acetylenes of ring size greater than 11 carbon atoms. Other cyclic alkynes should be easily prepared from the cyclic ketones. The preparation of cyclotetradecanone is well-documented[12] and cyclotetradecyne

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12) (a) G. Stork, T. L. MacDonald, J. Am. Chem. Soc., 97, 1264 (1975); (b) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, J. G. Thweat, J. Org. Chem., 29, 818 (1964).

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should be easily obtainable via this procedure. Cyclohexa-

decanone[13] and cyclooctadecanone[13b] have also been prepared.

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13) (a) E. P. Zinkevitch, I. K. Sarycheva, N. A. Preobrazhenshii, Zh. Org. Khim., 1, 1591 (1965); Chem. Abstr., 64, 612b; (b) ibid., 2, 2026 (1966); Chem. Abstr., 66, 75732m.

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Cyclopentadecyne and cycloheptadecyne have been prepared by an independent method.[14]

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14) L. Ruzicka, M. Hurbin, H. A. Boekenoogen, Helv. Chim. Acta, 16, 498 (1933).

_____

Cyclotrimerization of the Cyclic Acetylenes. Dialkyl acetylenic compounds trimerize with a number of catalysts to yield the hexalkylbenzene derivatives.[15] The two catalysts

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15) G. M. Whitesides, W. J. Ehmann, J. Am. Chem. Soc., 91, 3800 (1969) and references therein.

_____

found to give the highest yields for the cyclotrimerization cyclododecyne were dicobalt octacarbonyl[2] and titanium trichloride, prepared from titanium tetrachloride and tri-iso-butylaluminum. (Scheme I-3.)

Scheme I-3.

$$4 \longrightarrow 7a$$

$$Co_2(CO)_8 \qquad 85\%$$

$$TiCl_3 \qquad 92\%$$

$$4 \quad + \quad 18a \quad \xrightarrow{\quad TiCl_3 \quad} \quad 7a \qquad 18a$$

| 74% | 26% | | 74% of alkyne | 90% recovered |
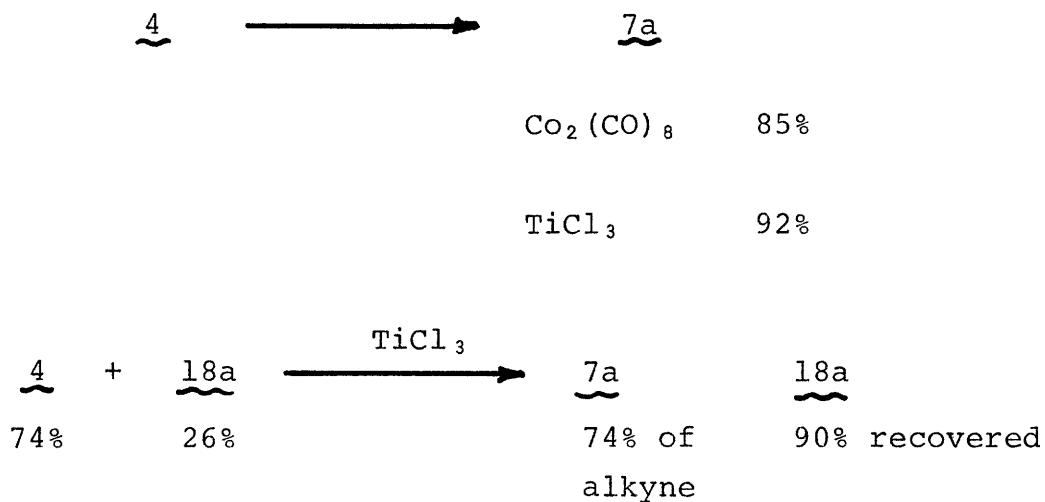
The yields for these reactions are quite good and the cyclotrimers are easy to prepare on hundred-gram scales. The physical properties of the cyclic acetylenes and their cyclo-trimers are given in Table I-I.

Table I-I. Physical properties of the cyclic acetylenes and their cyclotrimers.

Compound	Formula	bp(Torr)/mp	Analysis Carbon Hydrogen Found (Theory)
4	$C_{12}H_{20}$	119° (14)	Ref. 2
5	$C_{13}H_{22}$	140-2° (17)	Ref. 11c
6	$C_{15}H_{26}$	106-8° (1.0)	Ref. 14

Table I-I. (cont.)

7a	$C_{36}H_{60}$	165.6-6.0	87.77	11.95
			(87.73)	(12.27)[a]
7b	$C_{39}H_{66}$	199-201	87.34	12.31
			(87.56)	(12.43)
7c	$C_{45}H_{78}$	157.0-8.5	86.91	13.01
			(87.30)	(12.69)

(a) From ref. 2, p. 56.

Ozonolysis of the Cyclic Trimers of Cyclododecyne,
Cyclotridecyne and Cyclopentadecyne. The ozonolysis of
tris(decamethylene)benzene (7a) proceeds smoothly in
heptane, methylene chloride or methylene chloride/methanol
at 0°. The disappearance of starting material is easily
monitored by glpc.[16] The disappearance of 7a is a linear

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16) Analyses were performed on a 3% OV-17 column (3 ft)
operating at 300°.

---

function of the quantity of ozone added and slightly less
than two equivalents of ozone are required to effect complete
ozonolysis. Figures I-1 and I-2 show the disappearance of
tris(decamethylene)benzene (7a) with respect to added ozone
for two different solvent systems: methylene chloride and
heptane.

For the tris(hendacamethylene)benzene system a completely

different behavior is observed towards ozonolysis.
Ozonolysis of 7b under conditions identical to those which
effect complete cleavage of 7a results in less than a 10%
reduction in the amount of starting material present. As
the amount of ozone added is increased to cause complete
ozonolysis none of the desired products, cyclotridecane-1,2-
dione (10) or the corresponding macrocyclic tris-α-diketone
(11) can be found.

In the case of tris(tridecamethylene)benzene (7c)
the ozonolysis conditions which effect complete ozonolysis
of 7a are also effective here. The yields of isolated
products were somewhat lower, however, and will be discussed
later.

Derivatization of the Cyclic α-Diketones. The α-diketone
moieties which result from the ozonolyses of 7 were found to
be difficult to isolate and purify. They are sensitive to
base and light and are usually oils or low melting solids.
In light of these properties, it was determined that the
isolation of the α-diketonic species could be greatly
simplified through the preparation of a derivative prior to
isolation.

Many derivatives of cyclododecane-1,2-dione, 8, were
prepared (Table I-II) but only a few were crystalline, easily
isolable and formed in very high yield.

Figure I-I.   Ozonolysis of 7a in methylene chloride at 0°.
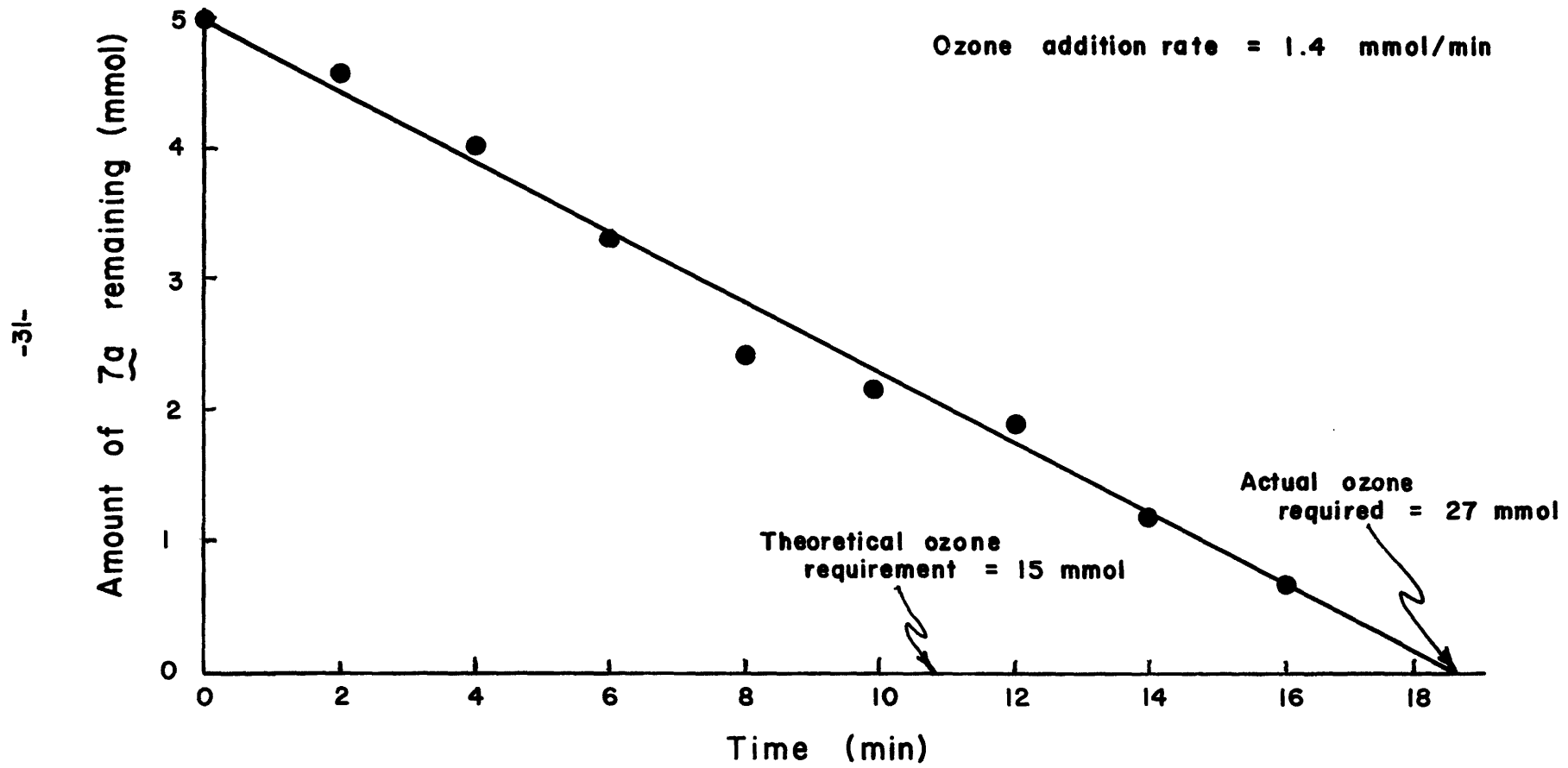
Figure I-2. Ozonolysis of 7a in n-heptane at 25°.
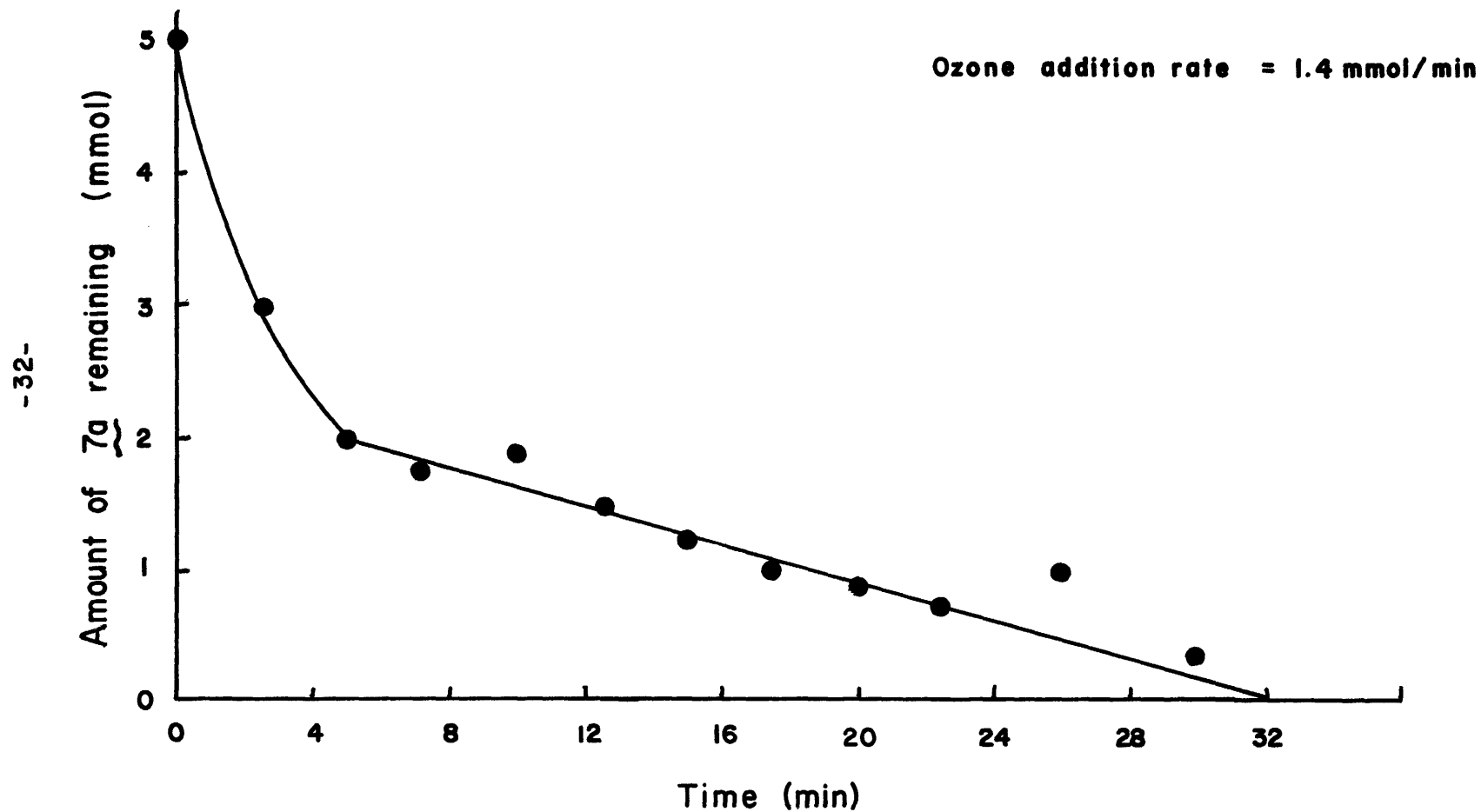
Table I-II. Derivatives of cyclododecane-1,2-dione.
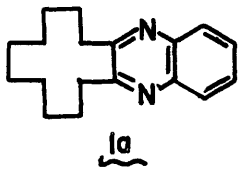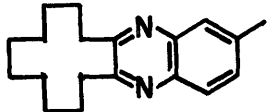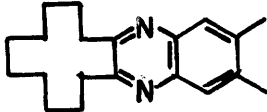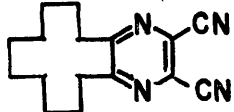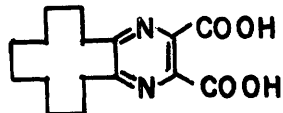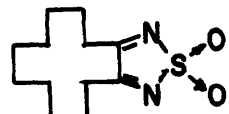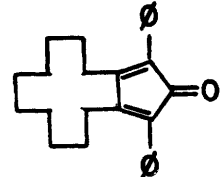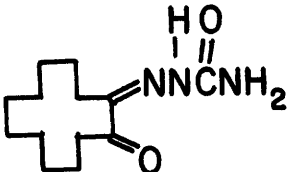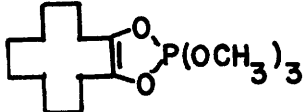
Derivative	Yield	Melting point	Reference to synthetic method
Ia	100%	84-5°	17
	100%	91-4°	17
	100%	117-8°	17
	75-84%	121.5-2.0°	18
		111-5°	19
	55%	140-3°	20
	80%	112-5°	21
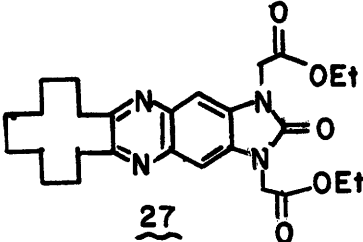
Table I-II. (cont.)
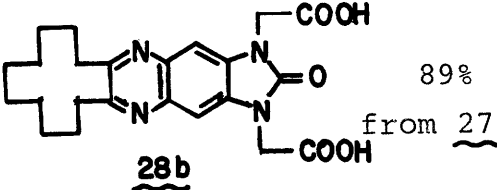
mono - DNP		200.0-0.8°	22
bis - DNP		295-6°	22
	100%	127-9° dec	23
	100%	unstable to air and water	24
27	100%	189-91°	
28b	89% from 27	>340°	

17) J. E. E. Simpson, "Chemistry of Heterocyclic Compounds,"
    J. E. E. Simpson, Ed., Interscience, 1953.

18) L. E. Hinckel, G. O. Richards, O. Thomas, J. Chem. Soc.,
    1432 (1937).

19) R. G. Jones, K. C. McLaughlin, Org. Syn., Coll. Vol. IV,
    824.

20) J. B. Wright, J. Org. Chem., 29, 1905 (1964).

21) J. R. Johnson, O. Grimmett, Org. Syn., Coll. Vol. III,
    806.

22) R. L. Shriner, R. C. Fuson, D. Y. Curtin, "The Systematic
    Identification of Organic Compounds," John Wiley and Sons,
    New York, N. Y., 1967, p. 126.

23) N. Minot, J.-P. M'Packo, Comptes rend., Ser. C, 270,
    1042 (1970).

24) F. Ramirez, Accounts Chem. Research, 1, 168 (1968);
    J. Am. Chem. Soc., 87, 543 (1965).

Of the derivatives prepared, the first one in Table I-II,
2,3-decamethylenequinoxaline (1a) had all of the desired

characteristics: it was easily purified and isolated and it

formed in quantitative yield. In addition, the reaction was

performed in weakly acidic solution (acetic acid or ethanol

with HCl catalyst) and required a very inexpensive derivatizing

agent, o-phenylenediamine. Many of the other derivatives were

crystalline materials which were easily purified but were

either formed in low yields or required difficultly obtained

derivatizing reagents. One derivative, the fourth in Table

I-II, 2,3-decamethylene-5,6-dicyanopyrazine, looked very

promising as a precursor to a water-soluble compound. The
yield for the condensation however, was low enough to be a
problem when the reaction was performed on the ozonolysis
product.

In light of these facts, it was decided the o-phenylene-
diamine derivative was the best one to prepare for isolation
and purification of the macrocyclic tris(α-diketone), 9.
The best method for the preparation of the derivative was
found to be reaction of the crude ozonolysis mixture (after
reduction and removal of the solvent) with excess o-phenylene-
diamine in either acetic acid or in ethanol with a catalytic
amount of added hydrochloric acid followed by column
chromatography of the resulting mixture. A tris(quinoxalino)
hexatriacontane could be isolated (3.7% yield) in this
manner which had mp 132.5-3.5° and gave the correct elemental
analysis. An independent ebullioscopic molecular weight
analysis gave a value of 650 (theory = 805) but I found
values of 800 and 840 for the molecular weight by a freezing
point depression of a solid solution of the macrocycle in
camphor.[25] The macrocyclic compound had an nmr spectrum

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25) L. F. Fieser, "Experiments in Organic Chemistry,"
     D. C. Heath and Co., Boston, Mass., 1957, p. 21.

_____

which was virtually identical to that of the o-phenylene-
diamine derivative of cyclododecane-1,2-dione and gave a

carbon-13 nmr which was in complete accord with the structure 1.

The carbon-13 spectral data are presented in Table I-III.

1
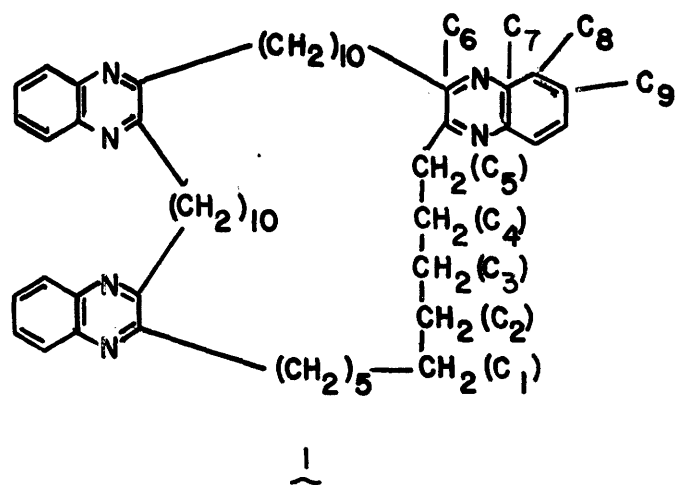
Table I-III. Carbon-13 nmr spectrum of 1.

Carbon atom	Ppm (downfield from TMS)
C_1	29.14
C_2	29.52
C_3	29.57
C_4	29.89
C_5	35.67
C_6	156.87
C_7	141.23
C_8	128.66
C_9	128.82

Optimization of the Ozonolysis Conditions. The
ozonolysis of tris(decamethylene)benzene (7a) proceeds

smoothly as far as the disappearance of starting material

is concerned. The appearance of product is however an entirely

different matter. Thus far, the maximum yields of cyclo-

dodecane-1,2-dione (isolated as the quinoxaline) obtained

are only about 12%.[26] It has been assumed that the formation

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26) Glpc yield: UCW-98 column (6 ft) operating at 250°.

---

of the macrocyclic compound directly parallels the formation

of the cyclododecyl compound. Therefore, when the yield of

cyclododecane-1,2-dione has been maximized, the yield of

macrocycle will have also been maximized. Unfortunately,

the macrocyclic trisquinoxaline derivative is formed in a

correspondingly lower yield, 3.7%.

Changing of many variables has not increased these yields.

Varying reaction times, reaction temperatures, solvent

polarity, solvent acidity, hydrogen donor capacity of the

solvent or solvent composition (when mixed solvent systems

are used) has very little effect on increasing the yield.

The results of these experiments are presented in Table I-IV.

From these experiments we have found the optimum reaction

solvent to be a protic solvent (methanol) containing large

quantities of methylene chloride to dissolve the cycloalkyne

cyclotrimer. The ozonolysis should be performed at 0° in the presence of a trace of acid (methane sulfonic acid) to catalyze formation of the hydroperoxymethoxy ketal. The amount of ozone required for complete ozonolysis of starting 7a is slightly less than two equivalents.

Table I-IV. Ozonolysis of tris(decamethylene)benzene.[a]

Solvent (ml)	Temp.	Time[b]	Additives	Unreacted Starting Material	Work-up[c]	Yield of 1a
CH_2Cl_2 (400)	-78°	8 hr		0%	Me_2S	5-10%
CH_2Cl_2 (400)	-78°	12 hr		0%	Me_2S	5-10%
CH_2Cl_2 (400)	-78°	24 hr		0%	Me_2S	5-10%
CH_2Cl_2 (400)	-78°	10 hr	MeOH (150 mmol)	0%	Std.	5%
CH_2Cl_2 (115) n-C_5H_{12} (250) $CF_2ClCFCl_2$ (35)	-78°	10 hr		0%	Std.	5%
CH_2Cl_2 (100) n-C_5H_{12} (300)	-78°	10 hr		0%	d	e
CH_2Cl_2 (250) MeOH (200)	0°	107 min	$MeSO_3H$ (2 drops)	0%	Std.	8%
CH_2Cl_2 (300) MeOH (100)	0°	2 hr		0%	Std.	1%

Table I-IV. (cont.)

CH_2Cl_2 (240)	0°	54 min		0%	Std.	10%
CH_2Cl_2 (250) MeOH (150)	0°	54 min	$MeSO_3H$ (15 mmol)	0%	Std.	12%
CH_2Cl_2 (200) $CF_2ClCFCl_2$ (200)	f	10 hr		0%	Std.	5%
CH_2Cl_2 (400)	0°	20 min		0%	Std.	6%
$n\text{-}C_7H_{16}$ (200)	25°	15 min		30%	Std.	2%
$n\text{-}C_7H_{16}$ (400)	25°	25 min		15%	Std.	7%
$n\text{-}C_7H_{16}$ (400)	25°	41 min		10%	Std.	8%
CH_2Cl_2 (350) MeOH (50)	0°	30 min	Na_2CO_3 (15 mmol)	0%	Std.	<1%
CH_2Cl_2 (150) $CHCl_3$ (25) MeOH (25)	-40°	2 hr		0%	g	<1%

(a) 5.0 mmol of tris(decamethylene)benzene was used for each reaction; (b) amount of ozone added = 1.4 mmol/min; (c) Std. work-up = 150 mmol of Me_2S, 2 drops of CF_3CO_2H, stir at 0° for 2 hr. All others used 150 mmol of Me_2S and no acid unless otherwise stated; (d) A solid precipitate which formed during the reaction was filtered and both the supernatant and solid were analyzed separately; (e) Yield in solid = 1%, yield in liquid = 7%; (f) Reaction was started at 0° and cooled to -78° after 3 min; (g) One equiv of $(MeO)_3P$ 10 equiv Me_2S.

Ozonolysis in Aprotic Solvents. Ozonolyses[27] can be

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27) For reviews see (a) L. Long, Chem. Rev., 27, 437 (1940);
     (b) P. S. Bailey, Chem. Rev., 58, 925 (1958); (c) A. T.
     Menyailo, Russ. Chem. Rev. (Engl.), 284 (1967); (d)
     W. Murray in "Techniques and Methods of Organic and
     Organometallic Chemistry," Vol. I, D. B. Denney, Ed.,
     Marcel Dekker, New York, N. Y., 1969, p. 1; (e)
     J. S. Belew in "Oxidation - Techniques and Applications
     in Organic Synthesis," Vol. I, R. L. Augustine, Ed.,
     Marcel Dekker, New York, N. Y., 1969, p. 259.

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performed in either protic or aprotic solvents.[28] In an

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28) R. H. Perry, J. Org. Chem., 24, 829 (1959).

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aprotic solvent, e.g. methylene chloride, an ozonide is formed.

In the case of tris(decamethylene)benzene, 7a, a trisozonide,

19, is the expected intermediate. (Scheme I-4.)

Scheme I-4.

19
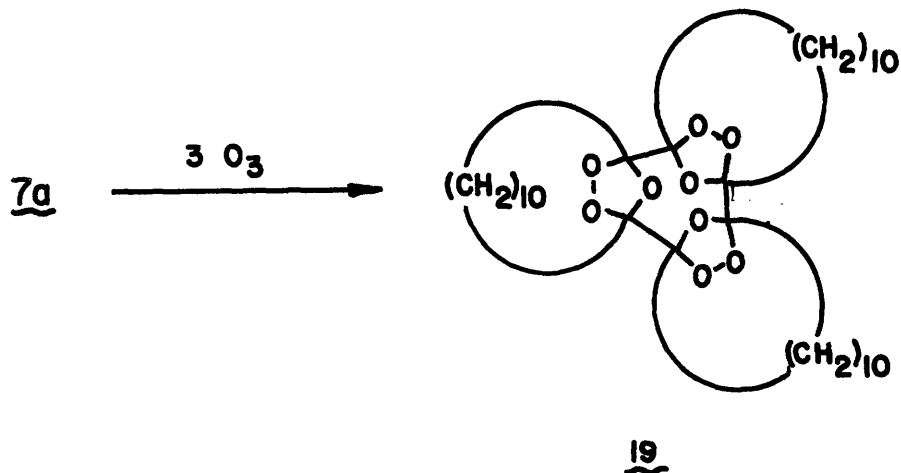
Reports in the literature of this type of intermediate

or diozonides in general are very scarce[29] and there is one

29) For ozonolysis of benzene and its derivatives or
conjugated systems see (a) A. A. Levine, A. G. Cole,
J. Am. Chem. Soc., 54, 338 (1932); (b) P. W. Haaijman,
J. P. Wibaut, Rec. Trav. Chim., 60, 842 (1941);
(c) J. van Dijk, Rec. Trav. Chim., 67, 945 (1948);
(d) J. P. Wibaut, Bull. Soc. Chim. France, 998 (1950);
(e) J. P. Wibaut, F. L. J. Sixma, Rec. Trav. Chim.,
71, 761 (1952); (f) G. M. Badger, Rec. Trav. Chim., 71,
468 (1952); (g) F. L. J. Sixma, J. P. Wibaut, Rec.
Trav. Chim., 71, 473 (1952); (g) J. P. Wibaut,
F. L. J. Sixma, J. W. F. Kampschmidt, H. Boer, Rec.
Trav. Chim., 69, 1355 (1952); (h) J. P. Wibaut,
Industrie Chim. Belge., 20, 3 (1955); (i) J. P. Wibaut,
Chimica (Switz.), 11, 298, 321 (1957); (j) J. P. Wibaut,
J. Chim. Phys., 53, 111 (1956); (k) N. A. Milas,
J. T. Nolan, P. P. H. L. Otto, J. Org. Chem., 23, 624
(1958); (l) J. P. Wibaut, J. van Dijk, Rec. Trav. Chim.,
65, 413 (1946); (m) J. P. Wibaut, F. L. J. Sixma,
Rec. Trav. Chim., 73, 797 (1954).

report the thermal decomposition of an α-hydroxyozonide[30] to

30) R. L. Cargill, B. W. Wright, J. Org. Chem., 40, 120 (1975).

yield a ketoacid via cleavage of the carbon-carbon bond between

the hydroxy and ozonide functionalities.

Ozonolysis in heptane. When the ozonolysis of 7a is

performed in pure heptane at -78° a white precipitate forms.

This white solid gives a negative test for active oxygen

(starch-iodide test paper) but work-up in the usual manner

yields none of the desired products. The solid is formed in

over 50% yield and is soluble in chloroform and THF. Low

temperature work-up (-40°) using trimethyl phosphite as the

reductant does not increase the yield. While identification

of the white solid has thus far eluded us, partially

ozonolyzed 7a seems to be a reasonable guess of its identity;

insolubility being the reason for incomplete ozonolysis.

Ozonolysis in methylene chloride. Methylene chloride

appears to be the best solvent (or cosolvent) for the

ozonolysis of 7a. The main drawback of this solvent is the

insolubility of 7a at -78°. At a concentration of 2.5 g/

400 ml the tris(decamethylene)benzene is still not completely

soluble at -78°. The ozonolysis proceeds smoothly but is

very slow at -78° (400-fold excess of O_3 is required).

Ozonolysis in a Protic Solvent. In a protic solvent,

e.g. methanol,[28,31] ozonolyses proceed via a different path-

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31)   (a) N. A. Milas, J. T. Nolan, Adv. in Chem., 21, 136
       (1959); (b) W. S. Knowles, Q. E. Thompson, J. Org. Chem.,
       25, 1031 (1960); (c) J. J. Pappas, W. P. Keaveney,
       E. Gancher, M. Berger, Tet. Letters, 4273 (1966); (d)
       P. L. Stotter, J. B. Eppner, Tet. Letters, 2417 (1973)

---

way than ozonolyses in an aprotic solvent.[32] In methanol,

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32)   For ozonolyses in acetic acid and other protic solvents
       see W. P. Keaveney, R. V. Rush, J. J. Pappas, Ind. Eng.
       Chem., 8, 89 (1969).

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the product after ozonolysis of a single double-bond of 7a
is shown by structure 20. (Scheme I-5.) Notice that the
intermediate is not an ozonide but rather a ketone and a
hydroperoxymethoxy ketal.

Scheme I-5.
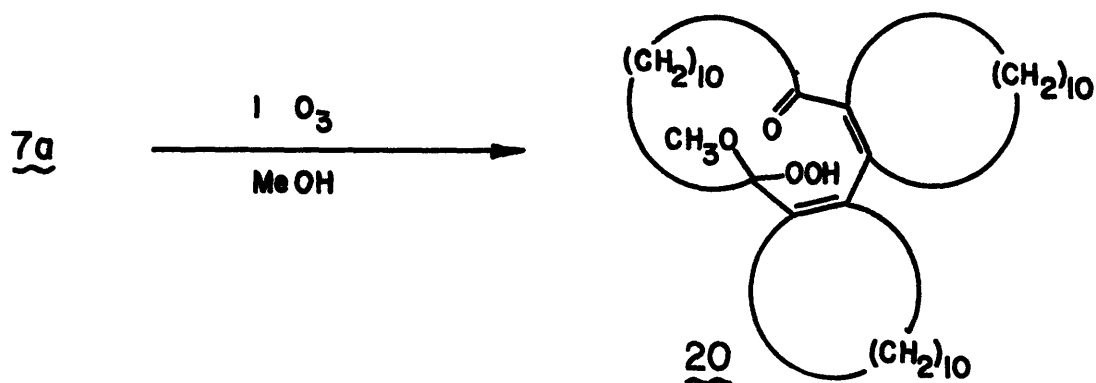
Cleavage of a second double-bond will now theoretically
produce a 50-50 mixture of 21a and 21b as shown in Scheme I-6.

Scheme I-6.
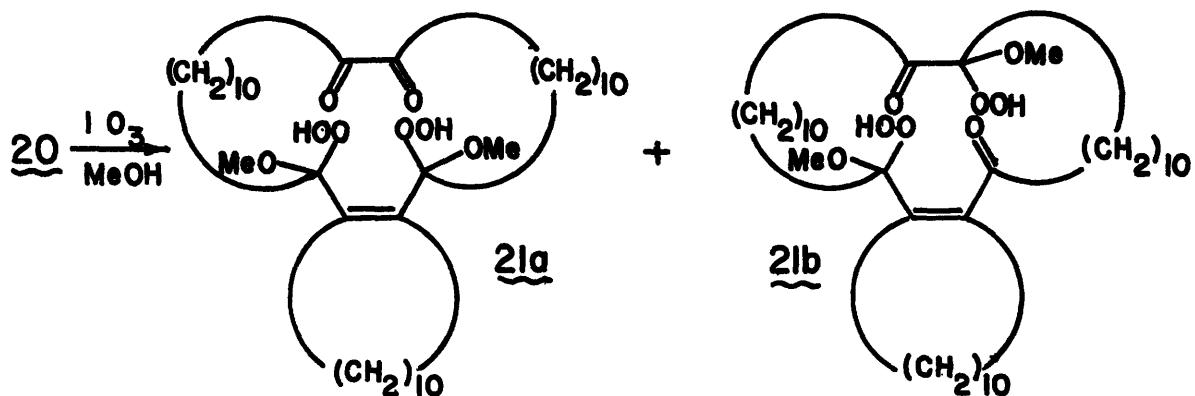
A problem arises at this point in the ozonolysis. One of the ozonolysis intermediates, 21a, contains an α-diketone moiety. Either ozone or a hydroperoxide functionality can attack the α-diketone in a number of ways as shown in Scheme I-7.[33]

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33) (a) P. Karrer, F. Haab, Helv. Chim. Acta, 32, 950 (1949);
(b) R. P. Barnes, J. Am. Chem. Soc., 57, 937 (1935);
(c) C. H. Hassall, Org. Reactions, 9, 73 (1957);
P. A. S. Smith in "Molecular Rearrangements," P. deMayo, Ed., Vol. I, Wiley-Interscience, New York, N. Y., 1963, p. 568.

Scheme I-7.
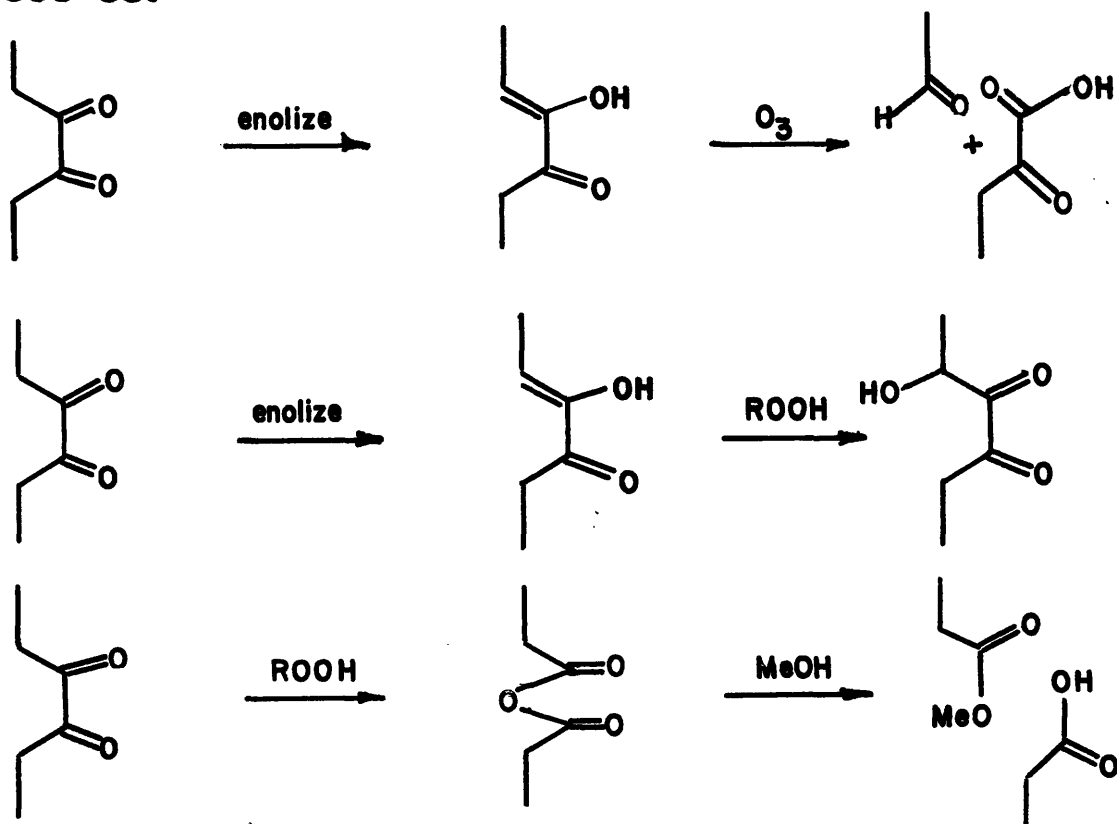
Due to these complications, it would seem that the ozonolysis should be performed in the absence of a protic solvent. We have found, however, that ozonolysis in an aprotic solvent, with care being taken to exclude all possible proton sources, does not increase the yield. The yield, in fact, is lowered when an aprotic solvent is used for the ozonolysis. The decomposition of α-diozonides has been discussed previously.

Ozonolysis in methanol/methylene chloride. Tris-(decamethylene)benzene is insoluble in methanol. Therefore, in order to perform the ozonolysis in this solvent, large amounts of methylene chloride must be added to effect solubilization. The solvent mixtures used ranged from 10 to 35% methanol: any mixture within this range has approximately the same effect on the products of the ozonolysis of 7a. This solvent system, along with a trace of methane sulfonic acid, has been found to be the best solvent for the ozonolysis of tris(decamethylene)benzene.

Reduction of Ozonolysis Mixtures. The reduction of the ozonolysis mixtures has been investigated very closely and several important facts have come to light. The initial ozonide formed, depicted as a cyclic, 5-membered trioxo species, is very stable towards reduction. Most of the common reducing agents, dimethyl sulfide,[31c-d,32] trimethyl phosphite,[31b,34]

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34) D. B. Denney, W. F. Goodyear, B. Goldstein, J. Am. Chem. Soc., 82, 1393 (1966).

sodium iodide,[35] glyoxylic acid[36] or sodium bisulfite[29k] only

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35) P. S. Bailey, R. E. Erickson, Org. Syn., Coll. Vol. V, 489.

36) P. Kolsaker, E. Bernatek, R. Johanson, R. Hytta,
Acta Chem. Scand., 27, 1526 (1973).

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reduce hydroperoxide functionalities. A few reducing agents,

lithium aluminum hydride,[37-39] sodium borohydride[38-39] and

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37) (a) F. L. Greenwood, J. Org. Chem., 20, 803 (1955);
(b) M. Hinder, M. Stoll, Helv. Chim. Acta, 33, 1308
(1950).

38) J. A. Sousa, A. L. Bluhm, J. Org. Chem., 25, 108 (1960).

39) (a) B. Witkop, J. B. Patrick, J. Am. Chem. Soc., 74,
3855 (1952); (b) R. Criegee, G. Schroder, Chem. Ber.,
93, 689 (1960).

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catalytic hydrogenation,[39] will reduce the ozonide directly.

The relative rates of reduction of the hydroperoxidic

functionality by phosphines, phosphites and sulfides have

been determined[40] and the following order of reducing power

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40) J. I. Shulman, Procter and Gamble Co., private communi-
cation.

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was found (most powerful reductant is listed first.) In

addition the reduction is acid catalyzed[41] and the addition

41) J. J. Pappas, private communication

$$R_3P > Ar_3P > (RO)_3P > (ArO)_3P > R_2S > R_2S \rightarrow O$$
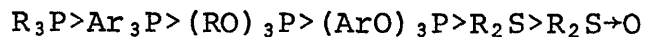
of only a trace of acid greatly increases the rate of
reduction.

Trimethylphosphite will reduce a hydroperoxide smoothly
and rapidly at -50° while dimethyl sulfide must be warmed to
at least 0°. For the case of a macrocyclic tris-α-diketone,
e.g. 9, the possibility exists that a hydroperoxide and an
α-diketone moiety may be present in the same molecule
simultaneously during reduction. The attack on an α-diketone
by hydroperoxide has been discussed previously (Scheme I-7).
In light of this possibility, it appears the reduction should
be carried out at the lowest temperature possible. Triphenyl-
phosphine appears to be the ideal reducing agent for this
system; it combines rapid reduction at low temperatures with
ease of handling and a lack of noxious odor. The main
drawback to the use of phosphines is their tendency to form
adducts with α-diketones which can then react further with
another ketone as shown in Scheme I-8.[24]

Scheme I-8.
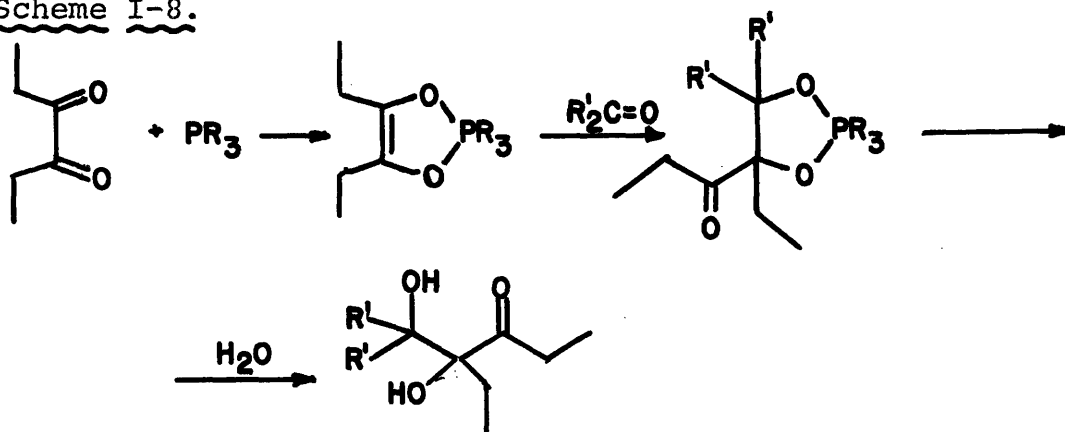
This undesirable side-reaction makes phosphines only marginally useful for the reduction of hydroperoxides to α-diketones. If the reduction can be carried out at a low enough temperature and with only one equivalent of phosphine this side-reaction could be avoided. In general, dimethyl sulfide has been used as the reducing agent; the few times that trimethylphosphite or triphenylphosphine have been tried no increase in yield was noted.

Reduction using metal hydrides or catalytic hydrogenation has been tried but these techniques generally yield vicinal diols or α-hydroxyketones.[42] I found that after reduction

42) (a) P. Ruggli, A. H. Lutz, Helv. Chim. Acta, 30, 1070
(1947); (b) L. A. Bigelow, H. G. Rule, W. A. P. Black,
J. Chem. Soc., 83 (1935); (c) M. Orchin, L. W. Butz,
J. Am. Chem. Soc., 65, 2296 (1943); (d) G. F. Hennion,
E. J. Watson, J. Org. Chem., 23, 656 (1958); (e)
E. E. Turner, L. Turner, J. Chem. Soc., 1761 (1952).

using these methods the isolation and derivatization of the

resulting compounds proved more difficult than for the corresponding α-diketones.

It appears then, that dimethyl sulfide is the reagent of choice for the reduction of the ozonolysis mixtures in this system. While the rate of reduction by dimethyl sulfide is much slower than phosphine, the presence of a trace of methane sulfonic acid in the ozonolysis mixture accelerates the reduction. Complete reduction can be effected in less than an hour at 0°.

Attempted Oxidation of 7a with Ruthenium Tetroxide. Ruthenium tetroxide oxidizes aromatic systems via cleavage of the aromatic nucleus to yield α-diketones.[43] Previous

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43)   (a) D. G. Lee, M. van den Engh in "Oxidation in Organic Chemistry," part B, W. S. Trahanovsky, Ed., Academic Press, Inc., New York, N. Y., 1973, p. 177; (b) S. Wolfe, S. K. Hasan, J. R. Campbell, Chem. Commun., 1420 (1970); (c) F. G. Oberender, J. A. Dixon, J. Org. Chem., 24, 1226 (1959); (d) D. M. Piatak, H. B. Bhat, E. Caspi, J. Org. Chem., 34, 112 (1969); (e) D. M. Piatak, G. Herbst, J. Wicha, E. Caspi, J. Org. Chem., 34, 116 (1969).

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work by Regen[2] and more recent experiments by the author show that tris(decamethylene)benzene is untouched by ruthenium tetroxide.

Preparation of a Water-Soluble Derivative. The solution of organic molecules in water is a problem of considerable interest to organic chemists. The synthesis of macrocyclic compounds with cavities large enough to enclose other smaller

organic molecules is one approach to the problem. If the

macrocyclic compound is soluble in water, then the hydrophobic

cavity in the interior of such a molecule can be a reasonable

vehicle for the solution of the second organic molecule in

water also. The cyclodextrins[44] represent the type of

44) (a) F. Cramer, H. Hettler, Naturwissen., 24, 625 (1967);
     (b) R. L. VanEtten, J. F. Sebastian, G. A. Clowes,
     M. L. Bender, J. Am. Chem. Soc., 89, 3242, 3253 (1967);
     (c) D. L. Vander Jagt, F. L. Killian, M. L. Bender,
     J. Am. Chem. Soc., 92, 1016 (1970); (d) F. Cramer,
     G. Mackensen, Angew. Chem. Intern. Ed. Engl., 5, 601
     (1966); (e) K. Freudberg, Angew. Chem., 47, 675 (1934);
     (f) D. French, R. L. MacIntire, J. Am. Chem. Soc., 72,
     5148 (1950); (g) F. Cramer, W. Saenger, H. Spatz,
     J. Am. Chem. Soc., 89, 14 (1967); (h) F. Cramer, W.
     Kampe, J. Am. Chem. Soc., 87, 1115 (1965); (i) D. French
     Adv. Carbohydrate Chem., 12, 250 (1957).

inclusion desired from the standpoint of catalysis or

preferential reactivity through inclusion.[45]

45) See ref. 1q for a discussion of these possibilities.

Other examples of inclusion of molecules or ions within

other molecules are found in the crown ethers and the molecular

sieves.[45] The crown ethers have already shown great utility

in the solution of inorganic salts in organic solvents while

the reverse process - - solubilization of an organic molecule

in water using a host-complex - - has been demonstrated only

for the cyclodextrins.

Several different routes were examined as methods for the solubilization of the macrocycle in water. In all of the methods tried, the cyclododecyl system was used as a model; it was assumed the macrocyclic compound would show similar solubility.

The simplest means of solubilization was to dissolve the quinoxaline derivative, 2,3-cyclododecylquinoxaline in acid. Quinoxalines are relatively weak bases; the pK_a of the protonated species being about 0.8.[46] 2,3-Decamethylenequinoxaline is

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46) Ref. 17, p. 228.

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soluble in 12N hydrochloric acid but addition of water caused precipitation of the starting quinoxaline.

The next method tried was alkylation of the decamethylene-quinoxaline to yield a quaternary ammonium salt. The literature holds reports of the alkylation of quinoxaline and various 2,3-disubstituted quinoxalines with methyl iodide[47a] or dimethyl

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47) (a) G. M. Bennett, G. H. Willis, J. Chem. Soc., 1960 (1928); (b) A. H. Cook, J. Garner, C. A. Perry, J. Chem. Soc., 710 (1942).

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sulfate.[47b] These methods, however, did not effect the quaternization of 2,3-decamethylenequinoxaline. Triethyl-oxonium tetrafluoroborate[48] alkylated both tertiary nitrogen

48) L. Fieser, M. Fieser, "Reagents for Organic Synthesis,"
Vol. I, John Wiley and Sons, Inc., New York, N. Y.,
1967, p. 1210.

atoms smoothly to yield 1,4-diethyl-2,3-decamethylenequinoxaline

bis(tetrafluoroborate) in fair yield. Unfortunately, the

derivative was insoluble in water and decomposed upon warming

to 60°.

The next attempt at solubilization of the quinoxaline

derivative involved oxidation to the di-N-oxide. Quinoxalines

are easily oxidized to the di-N-oxides with hydrogen peroxide.[49]

49) (a) G. T. Newbold, F. S. Spring, J. Chem. Soc., 519
(1948); (b) H. McIlwain, J. Chem. Soc., 323 (1943).

A similar procedure failed to produce the di-N-oxide of 2,3-

decamethylenequinoxaline.

Quinoxaline is oxidized by neutral potassium permanganate

to yield pyrazine-2,3-dicarboxylic acid.[17] This oxidation

procedure was successful on 2,3-decamethylenequinoxaline to

give 2,3-decamethylenepyrazine-5,6-dicarboxylic acid in 40%

yield. The diacid dissolved readily in dilute aqueous base

and appeared to be an excellent solubilizing moiety. When

the reaction was attempted with the macrocyclic trisquinoxaline,

1, only starting material was recovered in 92% yield. The

inertness of this compound is probably due to the fact that

the melting point of 1 is greater than 100° (132.5-3.5°)
and the solid material was not oxidized by boiling aqueous
potassium permanganate. Both quinoxaline and 2,3-decamethylene-
quinoxaline are liquids at 100° and are hence easily oxidized.
The next attempt at this type of oxidation was made using the
phase transfer technique of Sam and Simmons.[50] Dicyclohexyl-

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50) D. J. Sam, H. E. Simmons, J. Am. Chem. Soc., 94, 4024 (1972).

18-crown-6 was used as the catalyst in benzene solvent. This
procedure also resulted in unchanged starting material (98%).

In light of these failures, these routes were abandoned
and attempts were made at preparing other derivatives of the
cyclic α-diketones which could be readily rendered water-
soluble.

The first attempt made was condensation of the α-diketone
with diaminomaleonitrile (DAMN).[51] The condensation proceeded

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51) R. W. Begland, D. R. Hartter, F. N. Jones, D. J. Sam, W. A. Sheppard, O. W. Webster, F. J. Weigert, J. Org. Chem., 39, 2341 (1974).

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in fairly good yield (80%) with cyclododecane-1,2-dione and
hydrolysis of the resulting pyrazine dinitrile with aqueous,
refluxing KOH yielded a water-soluble material which was
identical to the material obtained from the potassium

permanganate oxidation of 2,3-decamethylenequinoxaline.
When the condensation was attempted on the ozonolysis product
mixture, no macrocyclic dicyanopyrazines could be isolated,
undoubtedly due to the fact that the less than quantitative
yield of condensed product with cyclododecane-1,2-dione was
greatly magnified when the same condensation was performed
three times on the same molecule. The low yield can be
attributed to the electron-withdrawing effect of the cyano
moieties in DAMN; the amino nitrogen are thus rendered
much less nucleophilic.

Several other attempts were made at synthesizing
compounds of type 22 but all met with dismal failure in the
synthesis or in condensation with the α-diketone compounds.

22a, X = COOR
22b, X = OR
22c, X = NH$_2$
22d, X = SO$_3$H
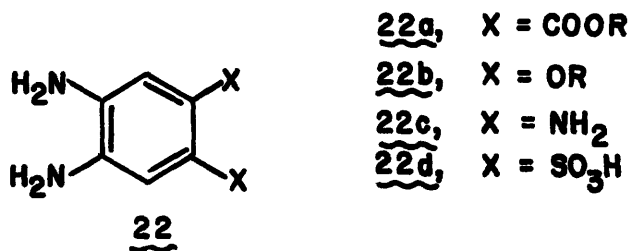
The following route was then found for the preparation
of a precursor to a water-soluble derivative. o-Phenylene-
diamine and urea condense in refluxing ethyl cellosolve to
yield benzimidazolone.[52] Benzimidazolone (23) can then be

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52) A. I. Smith, U. S. Patent 3,167,586, 1965; Chem. Abstr.,
     62, 9032 (1965).

nitrated using a variation of the method of Efros and El'tsov[53]

53) L. S. Efros, A. V. El'tsov, Zh. Obshch. Khim., 27, 127 (1957); Chem. Abstr., 51, 12882 (1957).

in good yield to give 5,6-dinitrobenzimidazolone (24). This compound can be bis-alkylated with ethyl bromoacetate in excellent yield to give the diethyl-5,6-dinitrobenzimidazolono-1,3-di-α-acetate (25). These reactions are outlined in Scheme I-9.

Scheme I-9.
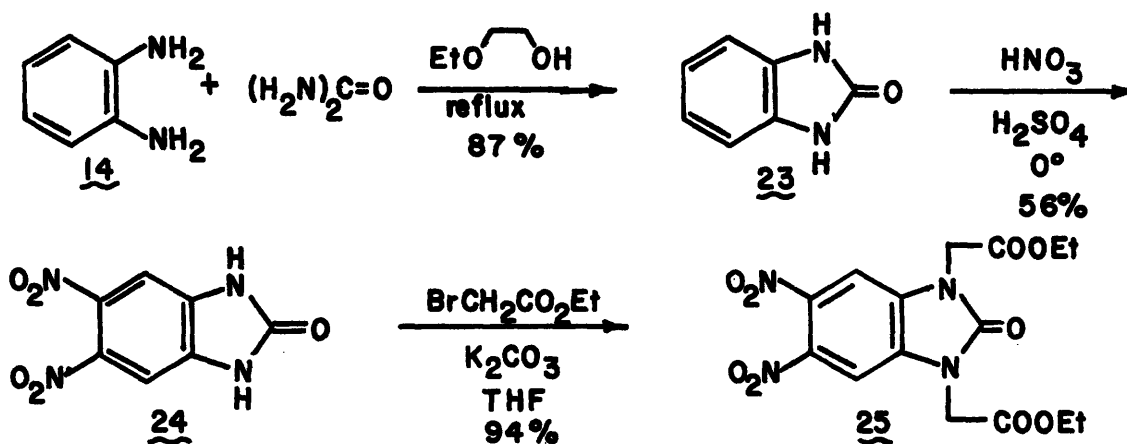
The resulting diester, 25, is then easily and quantitatively hydrogenated in acetic acid to yield the diamino compound, diethyl-5,6-diaminobenzimidazolono-1,3-di-α-acetate (26), which is then immediately condensed with cyclododecane-1,2-dione. (Scheme I-10.)

Scheme I-10.
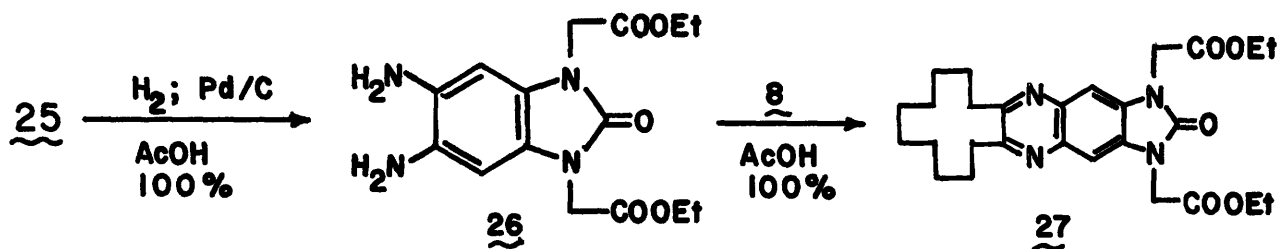
The hydrogenation is performed in acetic acid, the solvent of choice for the ensuing condensation with the α-diketone compounds. The diamino compound, 26, can therefore be filtered away from the hydrogenation catalyst directly into the crude ozonolysis product. After a brief period of refluxing (30 min) the acetic acid is removed at reduced pressure on a rotary evaporator and the resulting mixture is separated by column chromatography. A solid (2) with mp 307-9° can be isolated in this manner in 3.4% yield.

Saponification of the ethyl esters of 27 with KOH in refluxing water yield a dipotassium salt, 28, which is soluble to the extent of >1.0 g/100 ml in water at 25°. Similarly, the macrocyclic hexaester, 2, can be saponified to yield a hexapotassium salt, 29, which is also soluble to the extent of >1.0 g/100 ml in water at 25°. (Scheme I-11.)

Scheme I-11.

27 $\xrightarrow[\substack{H_2O \\ 89\% \\ 2.HCl}]{1.\ KOH}$

28a, dipotassium salt

28b, diacid

2 $\xrightarrow[\text{"}]{\text{"}}$

29
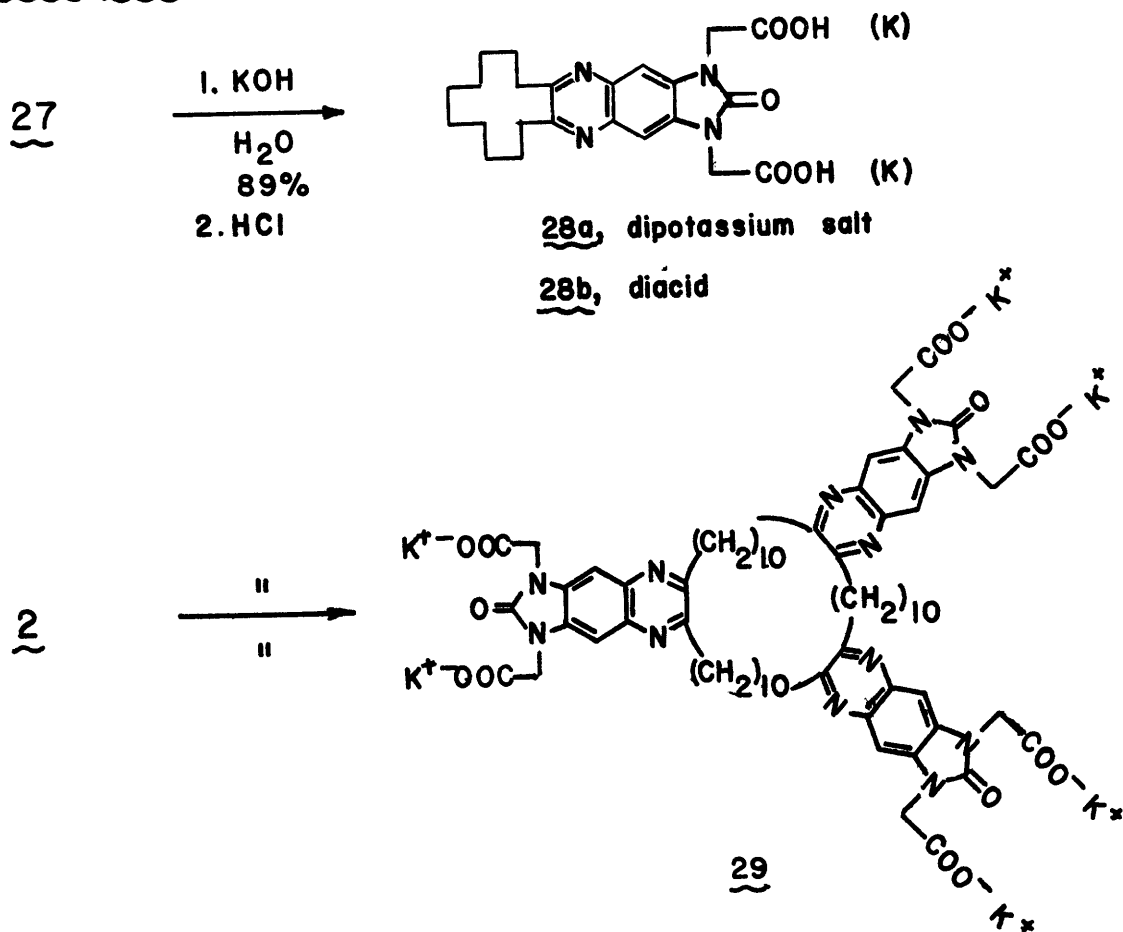
Conclusions

The cyclic trimers, compounds 7a, 7b, and 7c, of three cyclic acetylenes, 4, 5, and 6, have been ozonolyzed. Two of these trimers, 7a and 7c show about the same reactivity toward ozonolysis; they are completely ozonolyzed at 0° in methylene chloride/methanol with the addition of about two equivalents of ozone. The third, 7b, shows anomalous behavior. It is only about 65% ozonolyzed after the addition of 4 equivalents of ozone. The compounds 7a and 7c give the desired macrocyclic compounds, 1 and 3 in mediocre yield, 3.7 and 1.0% respectively while 7b, after ozonolysis and work-up, does not yield any macrocyclic products. The abnormal ozonolysis of 7b is as yet unexplained.

A precursor to a water-soluble macrocycle, 2, has been prepared. Saponification of the ester groups in this molecule lead to salts of the carboxylate functionalities in the molecule and yield a water-soluble macrocycle.

A new synthesis for cyclic acetylenes of ring size 12 or greater has been developed which yields the cycloalkyne in over 75% yield from the corresponding cyclic ketone. This synthesis should open a new range of cyclic acetylenes for the use of the synthetic chemist. Cyclic ketones have been prepared in good yield from the corresponding hydrocarbons[13] and this process could make the preparation of virtually any size cyclic acetylene a simple matter.

Experimental Section

General. Melting points were determined on a Thomas-
Hoover capillary melting point apparatus and are uncorrected.
Nuclear magnetic resonance spectra were recorded on a
Varian T-60 spectrophotometer; carbon-13 nmr spectra were
recorded on a Bruker HFX-90 spectrophotometer interfaced
with a Digilab FTS-NMR-3 data system operating in the Fourier
transform mode. Infrared spectra were taken on a Perkin-
Elmer model 567 spectrophotometer. Glpc analyses were
performed on a Perkin-Elmer model 990 gas chromatograph or
on a Hewlett-Packard model 810 gas chromatograph. Ultraviolet
spectra were recorded on a Gilford model 240 ultraviolet-visible
spectrophotometer. Microanalyses were performed by Midwest
Microlabs or Robertson Laboratory. Hydrogenations were
performed on a Parr Catalytic Hydrogenation Apparatus.

Cyclododecanone, o-phenylenediamine, ethyl bromoacetate,
phosphorus pentachloride, bromoform, 3,4-diaminotoluene,
4,5-dimethyl-o-phenylenediamine, epichlorohydrin, and 1,3-
diphenylacetone were purchased from the Aldrich Chemical Co.
Diaminomaleonitrile was purchased from PCR, Inc. Cyclopenta-
decanone was purchased from the Columbia Organic Chemical Co.
Cyclododecane was purchased from Chemical Samples Co. Potassium
t-butoxide was purchased from MSA Research Corp. Platinum
oxide and 10% palladium on carbon were purchased from
Englehard Industries. All solvents were reagent grade and

were used without further purification unless otherwise

noted.

1,1-Dichlorocyclododecane. Cyclododecanone (91 g,

0.50 mol) was dissolved in 450 ml of benzene or methylene

chloride. The solution was cooled in an ice bath to 5° and

phosphorous pentachloride (156 g, 0.70 mol) was added in one

portion with stirring.[54] Stirring was continued at 0° for

54) Best results are obtained with overhead stirring but a
Teflon-coated magnetic stirring bar may be used if a
powerful magnetic stirrer (e.g. Cole-Parmer 6 x 6) is
used.

4 hr and then the reaction was allowed to warm to room tempera-

ture and stirred for an additional 24 hr.[55] The reaction was

55) At this point the solution should show a virtually no
carbonyl peak in the ir. Additional phosphorous penta-
chloride may be added if necessary to effect total
conversion.

cooled to about 5° in an ice bath again and water (500 ml) was

added dropwise[56] with vigorous stirring. After addition of

56) The hydrolysis of the phosphorous oxychloride and excess
phosphorous pentachloride is very exothermic. Caution
should be exercised so that the reaction does not overheat.
Benzene is the recommended solvent from this consideration.

the water was complete, the mixture was stirred at 0° for
one hr and then allowed to warm to ambient temperature. The
mixture was stirred for an additional 24 hr and the organic
layer was separated and washed three times with 250 ml portions
of water. The organic layer was dried ($MgSO_4$) and the solvent
was removed at reduced pressure on a rotary evaporator at 25°
or less. 1,1-Dichlorocyclododecane was obtained as a pale
yellow oil, yield 116 g (97.5%), and was used without further
purification. The ir spectrum showed only a very small peak
(greater than 99% transmittance) in the carbonyl region.

Cyclododecyne (4). Dimethyl sulfoxide (1000 ml) was
degassed by bubbling a slow stream of prepurified nitrogen
through the stirred liquid at ambient temperature for 30 min.
Potassium t-butoxide (185 g, 1.65 mol) was added. The mixture
was stirred until most of the potassium t-butoxide had dissolved.
The solution was cooled in a water bath (20°) and 1,1-dichloro-
cyclododecane, prepared as previously described, was added in
one portion with vigorous stirring. The internal reaction
temperature did not exceed 50°. The dark red solution which
resulted was stirred at ambient temperature for 24 hr. A
mixture of ice and water (500 ml) was added and stirring was
continued for one hr at which time hexane (500 ml) was added.
The organic layer was separated, washed twice with 250 ml
portions of water and dried ($MgSO_4$). The hexane was removed
at reduced pressure on a rotary evaporator to yield a mixture

of cyclododecyne and 1,2-cyclododecadiene. Glpc analysis[57]

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57) Analysis was performed on a UCW-98 column (6 ft).

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showed these two compounds to be the only major components (>95%) of the mixture. The nmr spectrum was used to determine the relative amounts of allene and acetylene. The ratio of allene to alkyne was found to be 26/74. Distillation of the oil, bp 119°/14 Torr (lit.[5] 140°/40 Torr) afforded a mixture of cyclododecyne and cyclododeca-1,2-diene in the same ratio as previously and in 81% yield (66 g). Glpc analysis[57] showed the product consisted of greater than 99.5% of the allene-alkyne mixture.

Cyclopentadecyne (6). 1,1-Dichlorocyclopentadecane was prepared from cyclopentadecanone (26.4 g, 0.118 mol) in 98.5% yield in the same manner used for the preparation of 1,1-dichlorocyclododecane. Similarly, cyclopentadecyne was prepared from 1,1-dichlorocyclopentadecane in 79% yield after distillation (bp 168°/19 Torr; lit.[14] 158-9°/14 Torr) via a potassium t-butoxide elimination-isomerization as described for cyclododecyne. Nmr analysis showed no 1,2-cyclopentedecadiene present in the product.

13,13-Dibromobicyclo[10.1.0]tridecane. Cyclododecene (250 g, 1.50 mol) was dissolved in 750 ml of dry pentane with stirring. Potassium t-butoxide (185 g, 1.65 mol) was added

and the resulting slurry was cooled in an ice bath. Bromoform
(416 g, 1.65 mol) in 150 ml of pentane was added dropwise
over a 4 hr period to the stirred mixture. Water (200 ml)
was added and the organic layer was separated and washed
twice with 500 ml portions of water. The pentane solution
was dried over anhydrous $MgSO_4$ and the solvent was removed at
reduced pressure on a rotary evaporator. Distillation afforded
90 g (35%) of unreacted cyclododecene, bp 72-3°/0.4 Torr and
279 g (55%) of 13,13-dibromobicyclo[10.1.0]tridecane; bp 146-
7°/0.5 Torr (lit.[11c] 110-5°/0.08 Torr).

Cyclotrideca-1,2-diene. 13,13-Dibromobicyclo[10.1.0]tri-
decane (67.6 g, 0.20 mol) was dissolved in 500 ml of dry
ether and cooled to -78° with stirring under an atmosphere of
prepurified nitrogen. Methyllithium (110 ml, 2.0 M, 0.22 mol)
was added dropwise to the stirred solution. After addition
was complete, the mixture was allowed to warm to ambient
temperature. Water (500 ml) was added cautiously and the ether
layer was separated, washed twice with 500 ml portions of
water and dried over anhydrous $MgSO_4$. The solvent was removed
at reduced pressure on a rotary evaporator and the residual
oil was distilled to yield 11.2 g (32%) of 1,2-cyclotrideca-
diene; bp 142-5°/15 Torr (lit.[11c] 83-5°/3 Torr).

Cyclotridecyne (5). Cyclotrideca-1,2-diene (11.2 g,
0.063 mol) was dissolved in 120 ml of DMSO with stirring.
Prepurified nitrogen was bubbled through the solution for 30 min

at a slow rate. Potassium t-butoxide (7.8 g, 0.070 mol)
was added and the mixture was stirred at ambient temperature
under an atmosphere of nitrogen for 12 hr. The mixture was
then poured into 300 ml of water and extracted with 100 ml
of hexane. The organic layer was washed twice with 300 ml
portions of water and dried over anhydrous $MgSO_4$. The solvent
was removed at reduced pressure on a rotary evaporator and
the residual oil was distilled to yield 7.8 g (70%) of cyclo-
tridecyne; bp 140-2°/13 Torr (lit.[11c] 84-6°/3 Torr).

Tris(decamethylene)benzene (7a). (Cyclododecyne Cyclo-
trimer.) Dry, oxygen-free heptane (400 ml, distilled from
sodium benzophenone-dianion) was cooled to 0° in an ice bath
with stirring. Tri-iso-butylaluminum (13 ml of a 25% solution
in heptane) and titanium tetrachloride (1.3 ml, 2.2 g, 11 mmol)
were added via syringe to the cooled, stirred liquid. A
mixture of cyclododecyne and cyclododeca-1,2-diene, prepared
as described previously, (82 g, 0.50 mol) was added and the
mixture was allowed to warm to ambient temperature and stirred
for 24 hr under a positive pressure of prepurified nitrogen.
The reaction was quenched with 50 ml of methanol and poured
into 500 ml of water. Methylene chloride was added to dissolve
any 7a which had precipitated out. The organic layer was
separated, washed twice with 250 ml portions of water and dried
over anhydrous $MgSO_4$. The heptane and methylene chloride
were removed at reduced pressure on a rotary evaporator and

the residual solid was recrystallized from methyl ethyl ketone to yield 45 g (74%) of 7a; mp 166.5-7.0° (lit.[2] mp 161-3°). The yield was based on a starting composition of 4 that was 74% alkyne and 26% allene. The mother liquors from the recrystallizations were concentrated and distilled to yield cyclododeca-1,2-diene (19 g, 90%) which was present in the starting 4. 7a had nmr (CDCl$_3$) δ 1.57 (broad, 48H) and 2.60 (broad, 12H) and ir (KBr) 2930(vs), 2860(s), 1610(w), 1460(m), 1440(m), 1340(m), 725(m) cm^{-1}.

Tris(hendecamethylene)benzene (7b). (Cyclotridecyne Cyclotrimer.) Cyclotridecyne was cyclotrimerized in a manner entirely analogous to that for the cyclotrimerization of cyclododecyne to yield 7b (70%) which had mp 199-201°, nmr (CCl$_4$) δ 1.47 (broad, 54H) and 2.34 (broad, 12H) and ir (KBr) 2900(s), 2860(s), 1610(m), 1460(m), 1445(m), 1345(m), 1300(w), 1240(w), 710(m) cm^{-1}.

Anal. Calcd for C$_{39}$H$_{66}$: C, 87.56; H, 12.27. Found: C, 87.34; H, 12.31.

Tris(tridecamethylene)benzene (7c). (Cyclopentadecyne Cyclotrimer.) Cyclopentadecyne was cyclotrimerized in a manner entirely analogous to that for the cyclotrimerization of cyclododecyne to yield 7c in 72% yield which had mp 157.0-8.5°, nmr (CCl$_4$) δ 1.42 (broad, 66H), 2.44 (broad, 12H) and ir (CDCl$_3$) 2930(vs), 2860(s), 1455(s), 1350(m) cm^{-1}.

Anal. Calcd for C$_{45}$H$_{78}$: C, 87.30; H, 12.69. Found: C, 86.91; H, 13.01.

<u>2-Oximinocyclododecanone</u> and <u>Cyclododecane-1,2-dione</u> were prepared using the method of Kaufman.[1q]

<u>2,3-Decamethylenequinoxaline</u> (<u>1a</u>). Cyclododecane-1,2-dione (1.00 g, 5.1 mmol) and o-phenylenediamine (0.55 g, 5.1 mmol) were dissolved in 10 ml of absolute ethanol. Concentrated hydrochloric acid (0.1 ml) was added and the mixture was refluxed for 12 hr. Water (4 ml) was added to the hot solution and the mixture was cooled to 5°. The solid which crystallized was collected by filtration and dried to yield 1.33 g (100%) of 2,3-decamethylenequinoxaline. Recrystallization from ethanol afforded an analytical sample which had mp 84-5°, nmr (CDCl$_3$) δ 1.45 and 1.95 (broad, 16H total), 2.99 (t, 4H, J=7Hz), 7.70 (symmetrical m, 4H), ir (CDCl$_3$) 3060(w), 2930(s), 2860(s), 1480(m), 1465(m), 1445(m), 1395(m), 1350(m), 1205(m), 1120(m) cm^{-1} and uv λ$_{max}$ 241 nm (ε 30,000), 321 nm (ε 9,600).

<u>Anal.</u> Calcd for C$_{18}$H$_{24}$N$_2$: C, 80.54; H, 9.01; N, 10.43. Found: C, 80.62; H, 9.23; N, 10.25.

<u>2,3-Decamethylenequinoxaline</u> <u>dihydrochloride</u>. <u>Solubility</u> <u>in</u> <u>Water</u>. 2,3-Decamethylenequinoxaline (0.134 g, 0.50 mmol) was dissolved in 2 ml of concentrated hydrochloric acid. Hydrochloric acid (6 N) was added slowly with stirring. Visible turbidity appeared after the addition of about 25 ml of the dilute acid.

<u>Attempted</u> <u>Preparation</u> <u>of</u> <u>1,4-Dimethyl-2,3-decamethylene-</u>

quinoxaline. Methyl Iodide. 2,3-Decamethylenequinoxaline
(0.268 g, 1.00 mmol) and iodomethane (2.8 g, 20 mmol)
were heated at 90° in a sealed tube for 4 hr. Ether (10 ml)
was added and the solution was allowed to evaporate slowly.
The nmr spectrum of the residual oil did not show any of the
desired compound to be present. The major component appeared
to be starting material.

Attempted Preparation of 1,4-Dimethyl-2,3-decamethylene-
quinoxaline. Dimethyl Sulfate. 2,3-Decamethylenequinoxaline
(0.268 g, 1.00 mmol) and dimethyl sulfate (2.5 g, 20. mmol)
were heated in a sealed tube at 100° for 24 hr. The dimethyl
sulfate was hydrolyzed with 1 ml of water. Ethanol (10 ml)
was added and the mixture was allowed to evaporate slowly.
The nmr spectrum of the residual oil did not show any of the
desired compound to be present. The major component appeared
to be starting material.

1,4-Diethyl-2,3-decamethylenequinoxaline. Triethyloxonium
tetrafluoroborate[48] (1.90 g, 10.0 mmol) was stirred in 100 ml
of methylene chloride with 2,3-decamethylenequinoxaline
(0.268 g, 1.00 mmol) for 24 hr at ambient temperature. Methanol
(5 ml) was added to hydrolyze the excess alkylating agent and
the solvent was removed by distillation at reduced pressure.
Crystallization from ether afforded 0.11 g (30%) of product
with mp 166-70°. The material thus obtained decomposed upon
gentle warming in water (60°) and was therefore unsuitable as

a model for a water-soluble macrocycle.

Attempted Preparation of 2,3-Decamethylenequinoxaline-di-N,N'-oxide. 2,3-Decamethylenequinoxaline (0.268 g, 1.00 mmol) was dissolved in 4 ml of acetic acid. Hydrogen peroxide (30%, 1 ml) was added and the mixture was stirred at 55° for 24 hr. Water (10 ml) was added and the solid was separated by filtration. The nmr spectrum of the solid showed only starting material.

6-Methyl-2,3-decamethylenequinoxaline. 3,4-Diamino-toluene was condensed with cyclododecane-1,2-dione in a manner identical to that used in the preparation of 2,3-decamethylenequinoxaline to yield 6-methyl-2,3-decamethylene-quinoxaline (100%) which had mp 91-4° and nmr (CCl₄) δ 1.43 and 1.90 (broad, 16H), 2.52(s, 3H), 2.94(t, 4H, $\underline{J} = 8$ Hz), 7.2-7.8(m, 3H).

6,7-Dimethyl-2,3-decamethylenequinoxaline. 4,5-Dimethyl-o-phenylenediamine was condensed with cyclododecane-1,2-dione in a manner identical to that used for the preparation of 2,3-decamethylenequinoxaline to yield 6,7-dimethyl-2,3-decamethylene-quinoxaline (100%) which had mp 117-8° and nmr (CCl₄) δ 1.45 and 1.94 (broad, 16H), 2.47 (s, 6H), 2.97 (t, 4H, $\underline{J}$=7 Hz), 7.62 (s, 2H).

2,3-Decamethylenepyrazine-5,6-dicarboxylic Acid. Potassium Permanganate Oxidation of 2,3-Decamethylenequinoxaline. 2,3-Decamethylenequinoxaline (1.0 g, 3.4 mmol) was stirred

with 3.50 g (22.5 mmol) of potassium permanganate in 75 ml

of water at reflux for 6 hr. The mixture was cooled and

filtered. The aqueous solution was acidified with excess

concentrated HCl and placed in the refrigerator overnight.

The crystals which formed were collected by filtration to

give 0.43 g (41%) of 2,3-decamethylenepyrazine-5,6-dicarboxylic

acid which had mp 111-5° dec and nmr (CDCl$_3$ (3)/DMSO-d$_6$ (1))

δ 1.62 and 1.90 (broad, 16H), 2.97 (t, 4H, $\underline{J}$=7 Hz).

2,3-Decamethylene-5,6-dicyanopyrazine. Cyclododecane-1,2-

dione (0.98 g, 5.0 mmol) and diaminomalenonitrile (DAMN) (0.52 g,

5.0 mmol) were refluxed in 20 ml of ethanol and 10 ml of water

containing 5 drops of concentrated HCl for 5 min. The solution

was cooled and filtered to yield 1.05 g (3.9 mmol, 78%) of

product with mp 120-1°, nmr (CDCl$_3$) δ 1.55 and 1.87 (broad,

16H), 2.90 (t, 4H, $\underline{J}$=7 Hz), and ir (CDCl$_3$) 2930(s), 2850(s),

1520(m), 1445(m), 1375(s) cm^{-1}.

Anal. Calcd for C$_{16}$H$_{20}$N$_4$: C, 71.61; H, 7.51; N, 20.88.

Found: C, 71.86; H, 7.77; N, 20.60.

2,3-Decamethylenepyrazine-5,6-dicarboxylic Acid.

Hydrolysis of 2,3-Decamethylene-5,6-dicyanopyrazine. 2,3-

Decamethylene-5,6-dicyanopyrazine (0.54 g, 2.0 mmol) was

refluxed with KOH (0.065 g, 10.0 mmol) in 10 ml of water

was cooled to 5°. The crystals were collected by filtration

and air dried to yield 0.58 g (94%) of product which had

mp 111-5° and was in all other respects identical to the

material prepared by the potassium permanganate oxidation of 2,3-decamethylenequinoxaline.

2,3-Decamethylenepyrazine-5,6-dicarboxylate Dipotassium Salt. Potassium hydroxide (0.18 g, 2.9 mmol) was dissolved in 5 ml of water. 2,3-Decamethylenepyrazine-5,6-dicarboxylic acid (0.306 g, 1.00 mmol) was added and the mixture was stirred until all of the diacid had dissolved. The solution was concentrated at reduced pressure on rotary evaporator to approximately 1-2 ml and 30 ml of absolute ethanol was added. The precipitate was collected by filtration and air-dried to yield 0.25 g (74%) of the dipotassium salt, mp 320°.

Attempted Oxidation of Hexatriaconta[1,2,13,14,15,16-b,b',b"]trisquinoxaline (1) with Potassium Permanganate. Potassium permanganate (0.438 g, 2.79 mmol) and 1 (0.125 g, 0.155 mmol) were refluxed in 15 ml of water for 15 hr. The supernatant liquid was colorless at this point. The mixture was filtered hot and allowed to cool. Acidification of the aqueous solution after filtering yielded no recognizable products. Extraction of the manganese dioxide filtercake with THF yielded 0.115 g (92% recovery) of starting material.

Attempted Oxidation of 1 with Potassium Permanganate. Phase Transfer. Dicyclohexyl-18-crown-6 (0.01 g), 1(0.125 g, 0.155 mmol) and benzene (100 ml) were placed in a ball mill which was filled approximately 1/3 full with stones. Potassium permanganate (0.25 g, 1.5 mmol) was added and the

ball mill was rolled for 24 hr. The supernatant liquid was colorless at this point. Extraction of the benzene solution after filtration with 10% aqueous KOH and acidification of the aqueous layer yielded no recognizable products. Evaporation of the benzene solution at reduced pressure on a rotary evaporator yielded only 1 (98% recovery).

3,4-Decamethylene-1,2,4-thiadiazole-1,1-dioxide. Cyclododecane-1,2-dione (0.98 g, 5.0 mmol) and sulfamide (0.96 g, 10.0 mmol) were dissolved in 10 ml of absolute ethanol. Triethylamine (0.2 ml) was added and the mixture was refluxed for 24 hr with stirring. The solution was allowed to cool to ambient temperature and the white precipitate which formed was collected by filtration to yield 0.70 g of product with mp 140-3° and nmr (CF$_3$CO$_2$H) $\delta_{TMS(external)}$ 0.95 (broad, 16H), 1.95 (broad, 4H). The compound was not water-soluble and was not investigated further.

3,4-Decamethylene-2,5-diphenylcyclopentadienone. Cyclododecane-1,2-dione (0.98 g, 5.00 mmol) and 1,3-diphenylacetone (1.05 g, 5.0 mmol) were dissolved in 20 ml of hot absolute ethanol. KOH (0.2 g) was dissolved in 2 ml of ethanol and added through a reflux condenser to the stirred reaction mixture. The mixture was refluxed for 15 min and allowed to cool. Water (50 ml) was added and the precipitate was collected by filtration. The solid was recrystallized from ethanol to yield 1.5 g (80%) of the diphenylcyclopentadienone

derivative; mp 112-4.5° and nmr (CCl$_3$) δ 1.43 (broad, 20H),
7.22 (t, 10H, J=3 Hz).

Cyclododecane-1,2-dione Monosemicarbazone. Cyclododecane-
1,2-dione (0.98 g, 5.00 mmol) and semicarbazide hydrochloride
(1.12 g, 10.0 mmol) were dissolved in 10 ml of absolute
ethanol. The mixture was refluxed for one hr with stirring.
At this time the mixture was cooled to ambient temperature
and the white precipitate was collected by filtration to yield
1.5 g (100%) of the monosemicarbazone which had mp 258°.

Benzimidazolone (23) was prepared by the method of Smith.[52]

5,6-Dinitrobenzimidazolone (24) was prepared in a variation
of the method of Efros and El'tsov.[53] Benzimidazolone (67 g,
0.50 mol) was dissolved in 250 ml of concentrated sulfuric
acid. The dark solution was cooled to 5° in an ice bath and
90% nitric acid (white fuming, 67 ml) in 220 ml of sulfuric
acid was added dropwise to the cooled, stirred solution over
an 8 hr period. The reaction temperature was not allowed to
go above 10° during the addition. Immediately after the
addition of the nitric acid was complete the cold solution was
poured onto 3000 g of ice. The yellow solid which precipitated
was collected via filtration and washed thoroughly four times
with 1000 ml portions of cold water. Drying yielded 63 g
(56%) of 5,6-dinitrobenzimidazolone which was recrystallized
from 60% aqueous acetone to give crystals which melted at 344°
dec (lit.[53] mp >315°).

Diethyl-5,6-dinitrobenzimidazolone-1,3-di-α-acetate (25).

5,6-Dinitrobenzimidazolone (11.2 g, 0.050 mol) was dissolved

in 500 ml of THF. Potassium carbonate (13.8 g, 0.20 mol)

was added with vigorous stirring. Ethyl bromoacetate (20.0 g,

0.12 mol) was added and the mixture was refluxed for 48 hr.

The resulting mixture was filtered while hot and the solution

was concentrated on a rotary evaporator at reduced pressure.

Ethanol (95%, 100 ml) was added and the resulting crystals

were filtered and air-dried to yield 18.6 g (94%) of diethyl-

5,6-dinitrobenzimidazolone-1,3-di-α-acetate which had mp 201-2°,

nmr (CDCl$_3$) δ 1.32 (t, 6H, J = 8 Hz), 4.25 (q, 4H, J = 8 Hz),

4.97 (s, 4H), 7.66 (s, 2H) and ir (CDCl$_3$) 1740(s), 1620(w),

1540(s), 1510(m), 1410(m), 1340(s), 1205(s) cm^{-1}.

Anal. Calcd for C$_{15}$H$_{16}$N$_4$O$_9$: C, 45.46; H, 4.07; N, 14.14.

Found: C, 45.65; H, 4.30; N, 13.95.

Dimethyl-5,6-dinitrobenzimidazolone-1,3-di-α-acetate was

prepared from methyl bromoacetate and dinitrobenzimidazolone

in the same manner as the diethyl ester, 25, in 92% yield

with mp 211-4° and nmr (CD$_3$COCD$_3$) δ 3.94 (s, 6H), 4.95 (s, 4H),

8.04 (s, 2H).

5,6-Dinitrobenzimidazolone-1,3-di-α-acetic acid. To a

mixture of 25 (9.9 g, 0.025 mol) in 50 ml of water at 60° was

added sodium hydroxide (4.0 g, 0.10 mol) and the mixture was

stirred at 60° for one hr; all of the solid material had

dissolved. The warm solution was filtered and concentrated HCl

(17.7 ml, 0.2 mol) was added. The solution was cooled to 5°

and the crystals were collected via filtration and washed

twice with 20 ml portions of water. Drying yielded 7.6 g (89%)

of the diacid with mp 245-6° and nmr (DMSO-d$_6$) δ 4.78 (s, 4H),

8.23 (s, 2H).

Diethyl-5,6-diaminobenzimidazolone-1,3-di-α-acetate (26). 25
(1.98 g, 5.00 mmol) was dissolved in 60 ml of warm (60°) acetic

acid. 10% Pd on C catalyst (0.020 g) was added and the warm

mixture was hydrogenated at 451 psi of H$_2$ (uptake = 30 mmol

of H$_2$). The acetic acid solution of 26 thus prepared was

used without isolation or further purification after removal

of the catalyst via filtration.

Diethyl 1H,3H,2-oxoimidazo[4,5-g]cyclododeca[b]quinoxaline-
1,3-di-α-acetate (27). A solution of 26 (5.00 mmol) in 60 ml

of acetic acid prepared as described previously was filtered

into a flask containing 0.98 g (5.00 mmol) of cyclododecane-1,2-

dione. The resulting solution was stirred at ambient temperature

for one hr and then refluxed for one hr. The acetic acid was

removed at reduced pressure on a rotary evaporator and the

resulting solid was recrystallized from MEK/ethanol to yield

2.4 g (96%) of 27 with mp 189-91°, nmr (CDCl$_3$) δ 1.30 (t,

J=7 Hz), 1.50 and 2.13 (broad, 22H), 3.05 (t, 4H, J=7 Hz), 4.24

(q, 4H, J=7 Hz), 4.74 (s, 4H), 7.40 (s, 2H) and ir (CDCl$_3$)

2930(s), 2850(m), 1725(vs), 1600(w), 1485(m), 1430(m), 1350(m),

1205(s), 1195(s), 1015(m) cm^{-1}.

Anal. Calcd for $C_{27}H_{36}N_4O_5$: C, 65.30; H, 7.31. Found: C, 64.92; H, 7.50.

1H,3H,2-Oxomidazo[4,5-g]cyclododeca[b]quinoxalino-1,3-di-α-acetic Acid (28b). KOH (1.9 g, 30 mmol) and 27 (1.50 g, 3.00 mmol) were refluxed in 100 ml of water for 24 hr with stirring. The solution of 28a thus formed was filtered while hot and excess HCl (5 ml) was added. The mixture was allowed to cool to ambient temperature and the solid material was collected via filtration and air-dried to yield 1.07 g (2.44 mmol, 82%) of 28b with mp >340°, nmr (CDCl$_3$) δ 1.62 and 1.90 (broad, 16H), 2.97 (t, 4H, J=7 Hz) and ir (KBr) 2910(s), 2850(s), 2700-2500(m), 1710(vs), 1600(m), 1480(s), 1430(s), 1195(s), 840(w) cm^{-1}.

Preparative Scale Ozonolysis of 7a. (Preferred Method.) 7a (9.84 g, 20.0 mmol) was dissolved in 600 ml of methylene chloride. Methanol (200 ml) and methane sulfonic acid (2 drops) were added. The resulting solution was cooled to 0° in an ice bath with stirring. Ozone[58] (1.4 mmol/min) was bubbled

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58) The ozone was prepared using a Welsbach ozone generator operating at 4 psi of oxygen with a flow rate of 0.02 and at a potential of 80 V.

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through the cooled, stirred solution for 120 min (168 mmol of O$_3$, theory = 60 mmol). The ozone flow was stopped and pre-purified nitrogen was bubbled through the solution for 15 min.

Dimethyl sulfide (44.6 ml, 37.2 g, 600 mmol) was added and

the solution was stirred at 0° for an additional 2 hr. The

solvent was removed at ambient temperature and reduced

pressure on a rotary evaporator. The residual oil was

derivatized in one of the following ways.

2,3-Decamethylenequinoxaline (1b) and Cyclohexatriaconta-
[1,2,13,14,25,26-b,b',b"]trisquinoxaline (1). Condensation
of the Ozonolysis Product of 7a with 14. o-Phenylenediamine
(14) (12.96 g, 120.0 mmol) was added to the crude ozonolysis

product prepared as previously described. Absolute ethanol

(200 ml) and concentrated HCl (1 ml) were added and the

resulting solution was refluxed for one hr with stirring.

The solution was allowed to cool and the solvent was removed

at reduced pressure on a rotary evaporator. Hydrochloric

acid (4N, 300 ml) and methylene chloride (300 ml) were added

and the organic phase was separated. The methylene chloride

solution was washed twice with 300 ml portions of water and

dried over anhydrous $MgSO_4$. The solvent was removed at reduced

pressure on a rotary evaporator. The crude oil thus obtained

was dissolved in a minimum of chloroform and loaded on a

silica gel (Woelm, activity I, 0.063-0.2 mm, 225 g, column

dimensions: approx 4 x 50 cm) column and chromatographed as

described in Table I-V.

Table I-V. Column chromatography of the condensation

products of the ozonolysis product from 7a with 14.[a]

Eluent	Fraction	Volume (ml) of fraction	Compound[b] eluted	Weight (total)	Yield[c]
Hexane	1	1000	7a (0.15)	0.15 g	1.5%
2.5% THF/	2	1000	none	0.0 g	
Hexane	3	1000	?	1.9 g	
	4	1000	1a (1.6 g)	1.5 g	9.5%
	5	1000	?	0.35 g	
10% THF/	6	1000	?	0.7 g	
Hexane	7	1000	?	0.7 g	
20% THF/	8	1000	1 (0.63 g)	1.1 g	3.7%
Hexane	9	1000	?		

(a) The silica gel was packed into the column using a slurry in hexane. (b) The weight of the pure compound is in parentheses. (c) The yields are based on 60 mmol of 1a = 100% and 20 mmol of 1 = 100%.

Compound 1 had nmr (CDCl$_3$) δ 1.55 (broad, 48H), 3.02

(distorted t, 12H), 7.81 (symmetrical m, 12H), ir (KBr)

3060(w), 2930(s), 2860(s), 1485(m), 1465(m), 1390(m), 1340(m),

1205(m) and uv λ_{max} 241 nm (ε 84,000) and 319 (ε 26,000) and

had mp 132.5-3.5°.

Anal. Calcd for C$_{54}$H$_{72}$N$_6$: C, 80.54; H, 9.01; N, 10.43.

Found: C, 80.58; H, 8.88; N, 10.29.

Compound 1a had spectral and analytical data in complete

accord with the results described earlier.

Ozonolysis of 7a. (General Techniques.) A quantity of
7a was dissolved in the appropriate solvent as described in
Table IV. The solution was cooled to the desired temperature
and the necessary additives were added. Ozone[58] was bubbled
into the cooled, stirred solution for the prescribed period
of time and then dimethyl sulfide (10-fold excess), methanol
(50 ml) and trifluoroacetic acid (2 drops) were added. The
solution was then stirred at 0° unless stated otherwise.
The solvent was removed at reduced pressure on a rotary
evaporator at the lowest temperature possible and the crude
oil was dissolved in 150 ml of absolute ethanol. o-Phenylene-
diamine (2-fold excess) and concentrated HCl (1 ml) was added
and the resulting solution was refluxed for two hr. The
yield of 1a was determined by glpc.[57]

Diethyl 1H,3H,2-oxoimidazo[4,5-g]cyclododeca[b]quinoxaline-
1,3-diacetate (27) and Cyclohexatriaconta[1,2,13,14,25,26-
b,b',b"]tris(diethyl 1H,3H,2-oxoimidazo[4,5-g]quinoxalino-1,3-
di-α-acetate) (2). Condensation of the Ozonolysis Product of
7a with 25. 25 (60 mmol) in 750 ml of acetic acid was prepared
as previously described. 7a (20 mmol) was ozonolyzed as
previously described and the acetic acid solution of 26 was
filtered directly into the crude ozonolysis product. The
solution was refluxed with stirring for one hr. Most of the
acetic acid was removed at reduced pressure on a rotary
evaporator. Hydrochloric acid (4N, 300 ml) and methylene

chloride (300 ml) were added. The organic phase was separated, washed twice with 300 ml portions of water, dried (MgSO$_4$) and concentrated at reduced pressure on a rotary evaporator. The residual oil was dissolved in a minimum of chloroform and loaded on a silica gel (Woelm, activity I, o.063-0.2 mm, 225 g, column dimensions: approx 4 x 50 cm) column and chromatographed as described in Table I-VI.

Table I-VI. Column chromatography of the condensation products of the ozonolysis product from 7a with 25.[a]

Eluent	Fraction	Volume (ml) of fraction	Compound[b] eluted	Yield
Benzene	1	1000		
	2	1000		
5% THF/ Benzene	3	1000		
	4	1000	27 (2.2 g)	
10% THF/ Benzene	5	1000 ⎱		7.5%
	6	1000 ⎰	27	
20% THF/ Benzene	7	1000		
	8	1000	2 (0.99 g)	3.4%
50% THF/ Benzene	9	1000	2	
	10	1000		

(a) The Silica gel was packed into the column using a slurry in benzene. (b) The weight of the pure, isolated compound is in parentheses. (c) The yields are based on 60 mmol of 27 = 100% and 20 mmol of 2 = 100%.

Compound 27 had spectral and analytical data in complete accord with the data described earlier. Compound 2 had nmr

(CDCl$_3$) δ 1.32 (t, J=7 Hz), 1.55 and 2.17 (broad, 22H),

3.07 (t, 4H, J=7 Hz), 4.27 (q, 4H, J=7 Hz), 4.87 (s, 4H),

7.56 (s, 2H) and ir (KBr) 3060(w), 2930(s), 2860(s), 1720(vs),

1585(m), 1470(m), 1435(m), 1380(m), 1335(m) 1205(s), 1180(s),

1020(m), 925(m), 840(m) cm^{-1} and had mp 307-9°.

2,3-Tridecamethylenequinoxaline and Cyclopentatetraconta-
[1,2,16,17,31,32-b,b',b"]trisquinoxaline (3). Ozonolysis of
7c and Condensation with 14. A solution of 7c (6.19 g, 10.0

mmol) in 300 ml of methylene chloride and 100 ml of methanol

was prepared. Methane sulfonic acid (2 drops) was added and

the stirred solution was cooled to 0°. Ozone was bubbled

into the solution in the same manner used for the ozonolysis

of 7a, and the reduction and isolation of the crude ozonolysis

product was done in the identical fashion as described for 7a.

o-Phenylenediamine (14) (6.48 g, 60.0 mmol), ethanol

(200 ml) and concentrated HCl (1 ml) were added to the crude

ozonolysis product and the mixture was treated in the same

manner as described for the preparation of la and 1. Column

chromatography on 225 g of silica gel as described for la and

1 in Table I-V afforded 2,3-tridecamethylenequinoxaline which

was eluted in fraction 4 and 3 which was eluted in fraction 8.

Recrystallization of these fractions from ethanol-water

afforded 0.38 g (4%) of 2,3-tridecamethylenequinoxaline with

mp 47.5-8.5°, nmr (CDCl$_3$) δ 1.57 (broad, 22H), 3.04 (distorted

t, 4H), 7.78 (symmetrical m, 4H) and ir (KBr) 3060(w), 2920(vs),

2850(s), 1735(w), 1620(m), 1560(w), 1480(m), 1460(s), 1395(m),

1350(m), 1205(m), 1125(m), 760(s) cm^{-1} and 0.090 g (0.9%,

10 mmol = 100%) of 3 with mp 139-41°, nmr (CDCl$_3$) 1.32 (broad,

66H), 3.05 (distorted t, 4H), 7.83 (symmetrical m, 4H) and

ir 2920(s), 2850(s), 1630(m), 1525(m), 1460(m), 760(m) cm^{-1}.

Anal. Calcd for $C_{21}H_{30}N_2$: C, 81.24; H, 9.74; N, 9.02.

Found: C, 80.01; H, 9.87; N, -----. Calcd for $C_{63}H_{90}N_6$:

C, 81.24; H, 9.74; N, 9.02. Found: C, 81.22; H, 9.74; N, 8.88.

Ozonolysis of 7b. A solution of 7b (5.34 g, 10.0 mmol)

in 300 ml of methylene chloride and 100 ml of methanol was

prepared. Methane sulfonic acid (2 drops) was added and the

stirred solution was cooled to 0° in an ice bath. Ozone[58]

(1.4 mmol/min) was bubbled through the solution for 2 hr

(168 mmol). The solution was flushed with prepurified

nitrogen for 15 min and dimethyl sulfide (22.3 ml, 18.6 g,

300 mmol) was added. The solution was stirred at 0° for two

hr and worked-up as described in the procedure for the

ozonolysis of 7a.

Absolute ethanol (200 ml) was added to the crude

ozonolysis product and the resulting mixture was filtered

to give 1.8 g of starting 7b (34% recovery). o-Phenylene-

diamine (14) (6.48 g, 60.0 mmol) and concentrated HCl (1 ml)

were added and the mixture was treated in the same manner as

described for the condensation of 1a and 1 with 14. The

resulting oil was column chromatographed on 225 g of silica

gel as described in Table I-V for the isolation of 1a and 1

yielded a trace of 2,3-hendecamethylenequinoxaline in

fraction 4. None of the desired macrocycle could be detected.

The Elucidation of the Mechanism of Oxidation

by Adams' Catalyst

Adams' catalyst,[1] reduced platinum oxide, is a useful

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1) R. Adams, V. Voorhees, R. L. Shriner, Org. Syn., Coll. Vol. I, 463 (1941).

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catalyst for the oxidation of alcohols by molecular oxygen.[2]

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2) K. Heyns, H. Paulsen in "Newer Methods of Preparative Organic Chemistry," W. Foerst, Ed., Vol. II, Academic Press, New York, N. Y., 1963, p. 303.

Primary alcohols are oxidized to aldehydes in non-aqueous solvents and to acids in water. Secondary alcohols are oxidized to ketones at a rate slower than that for primary alcohols. The oxygen in the reaction is reduced to water.

Several incentives exist for the investigation of this oxidation. The oxidation is extremely selective and therefore potentially very useful. Primary alcohols are oxidized preferentially to secondary alcohols. Polyhydroxy compounds, for example carbohydrates, can often be oxidized with high positional selectivity. For example, L-sorbose (1) can be oxidized to 2-keto-L-gulonic acid (2) in 60% yield.[3] Similarly

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3) K. Heyns, Justus Liebigs Ann. Chem., 558, 171, 177 (1953).

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myo-inositol (3) can be oxidized to a monoketone, 2-myo-

HO—, HO—, HO, O, OH, CH$_2$OH, 1

Pt/C
O$_2$
50°
60%

HO—, HO—, HO, O, OH, COOH, 2
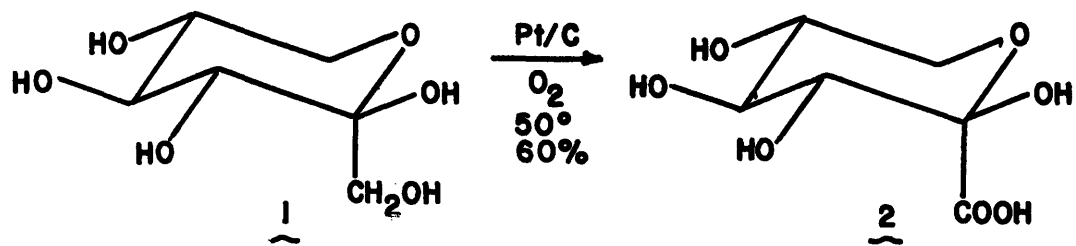
inosose (4) in good yield.[4] In this case, the solitary

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4) K. Heyns, H. Paulsen, Chem. Ber., 86, 833 (1953).

OH, HO—, HO—, HO, OH, H, axial, OH, 3

Pt
O$_2$

OH, HO—, HO—, HO, OH, O, 4
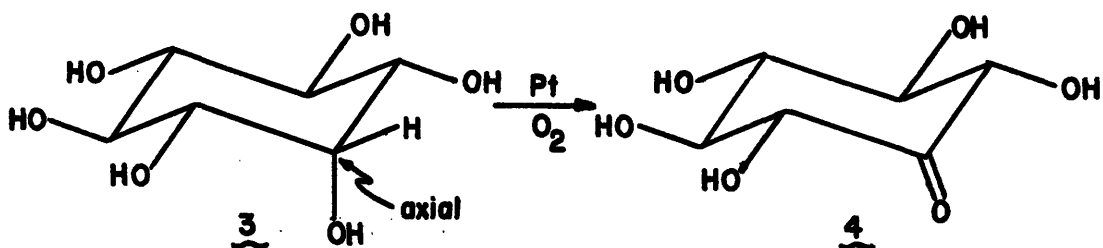
axial alcohol is oxidized preferentially and is the only

alcohol oxidized. Pentaerythritol (5) can be oxidized to

a monocarboxylic acid, trimethylolacetic acid (6) with Adams'

catalyst in the presence of one equiv of base.[5] This

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5) K. Heyns, M. Beck, Chem. Ber., 89, 1648 (1956).

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transformation can occur since the intermediate aldehyde

is more easily oxidized than a primary alcohol in the presence

of base and the carboxylate functionality retards the rate of

oxidation of a second alcohol moiety.

Many other examples of selective oxidation of primary

alcohols to aldehydes[6-8,21], selective oxidation of polyhydroxylic

6) A. Strecker, Justus Liebigs Ann. Chem., 93, 370 (1955).

7) H Delaby, Compt. rend., 182, 140 (1926).

8) P. Karrer, W. Hess, Helv. Chim. Acta, 40, 265 (1957).

compounds,[9-11] oxidation of secondary alcohols,[12-13] oxidation

9) J. W. E. Glattfield, S. Gershon, J. Am. Chem. Soc., 60, 2013 (1938).

10) K. Heyns, M. Beck, Chem. Ber., 91, 1720 (1958).

11) S. Okuo, J. Pharm. Soc. Japan, 47, 1395 (1954).

12) B. Lindberg, B. Wickberg, Arkiv Kemi, 13, 447 (1959).

13) S. J. Angyal, L. Anderson, Adv. Carbohydrate Chem., 14, 135 (1959).

of amino alcohols,[14-15] and oxidation of steroidal alcohols[16-17]

14) K. Heyns, M. Paulsen, Chem. Ber., 89, 1152 (1956).

15) C. H. Engster, P. G. Waser, Helv. Chim. Acta, 40, 888 (1957).

16) R. P. A. Sneeden, R. B. Turner, J. Am. Chem. Soc., 77, 130, 190 (1955).

17)   (a) L. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold, New York, N. Y., 1949, p. 126;   (b) J. Schrieber, A. Eschenmosher, Helv. Chim. Acta, 38, 1529 (1955).

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can be found in the literature.

A second stimulus for the elucidation of the mechanism of this oxidation is the short catalyst lifetime. In general, procedures require a high catalyst to substrate ratio of 0.1 by weight. We have found that catalyst lifetime is very short (hours) and oxidations rarely go to completion. For example, the oxidation of isopropanol to acetone normally goes in yields of less than 50%. A good understanding of the mechanism should give insight into why the catalyst becomes inactive and why large amounts of catalyst are required.

The first step in defining a mechanism is to identify the reaction under investigation. The overall balanced equation for the oxidation is given in the following equation.

$$R_2CHOH \quad + \quad 1/2O_2 \quad + \quad nPt(n) \quad \longrightarrow$$

$$R_2C=O \quad + \quad H_2O \quad + \quad nPt(n).$$
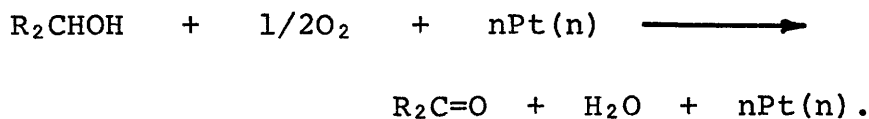
The oxidation-reduction reactions may be expressed as

$$2H^+ \quad + \quad 1/2O_2 \quad + \quad 2e^- \quad \longrightarrow \quad H_2O$$

$$R_2CHOH \quad \longrightarrow \quad R_2C=O \quad + \quad 2H^+ \quad + \quad 2e^-$$

$$nPt(n) \quad \longrightarrow \quad nPt(n).$$
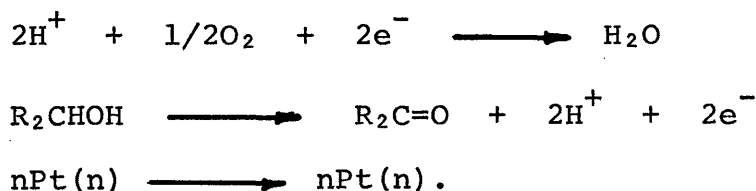
The oxidation and reduction of platinum species during the course of the reaction is a distinct possibility. The question of what platinum species is actually involved in the reaction is one of major importance. The possibility exists for redox systems of the following type.

$$2H^+ + Pt(0) + 1/2O_2 \longrightarrow Pt(II) + H_2O$$
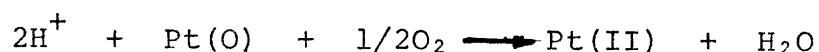
This oxidation of platinum is well within the realm of plausibility. The presence of platinum(II) species within the reaction mixture creates the possibility for platinum alkoxide intermediates.

$$Pt(II) + 2ROH \longrightarrow (RO)_2Pt + 2H^+$$

In view of these facts, several plausible mechanisms can be proposed. The simplest of these we will call the "dehydrogenation" mechanism. This mechanism involves a dehydrogenation of the alcohol over an active platinum surface to yield a carbonyl compound and platinum-bound hydrogen atoms. The dehydrogenation may proceed through a radical as shown in Scheme II-1A or _via_ loss of hydride as in Scheme II-1B. For simplicity, all adsorption or desorption steps will be omitted in the following mechanisms.

Scheme II-1A
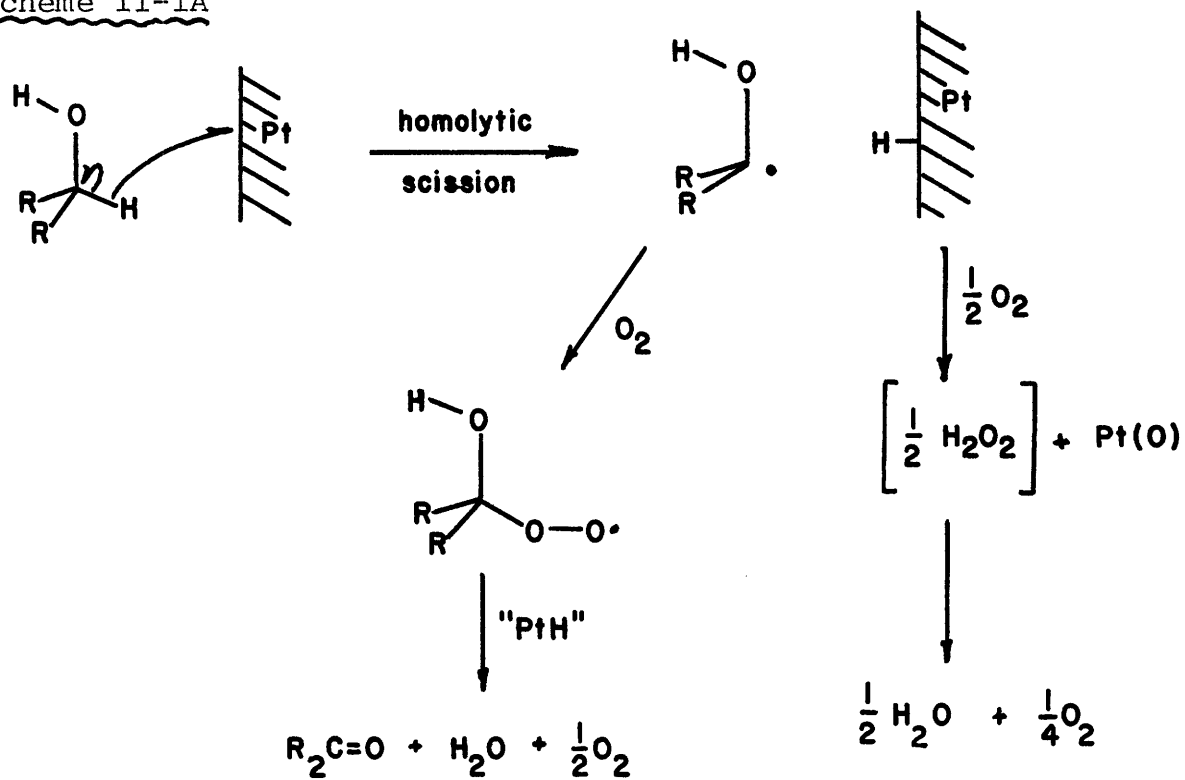
Scheme II-1B
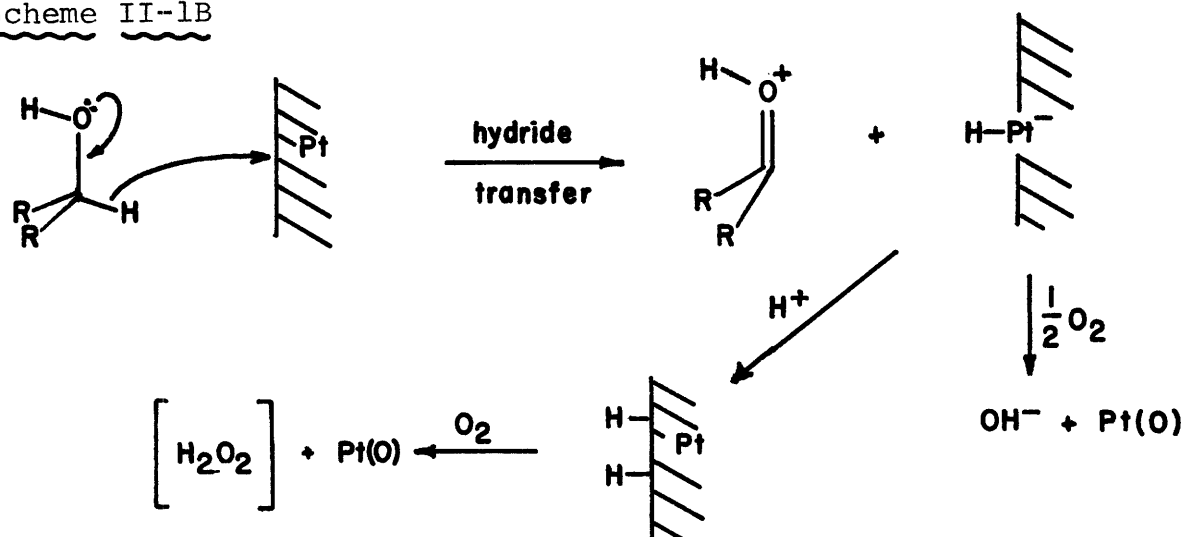
A second mechanism invokes "activated" oxygen on a platinum surface as the oxidizing agent. Oxygen is dissociatively adsorbed on platinum black to give surface bound oxygen atoms.[18] This "active" oxygen

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18) (a) W. M. H. Sachtler, Catal. Rev., 4, 27 (1970);
    (b) G. K. Boreskov, Adv. Catal., 15, 286 (1964); (c)
    Private communication with P. A. Kilty, Shell
    Development Co.,

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can then either abstract a hydride as shown in Scheme II-2A or abstract a hydrogen radical as outlined in Scheme II-2B.

Scheme II-2

Scheme II-2A
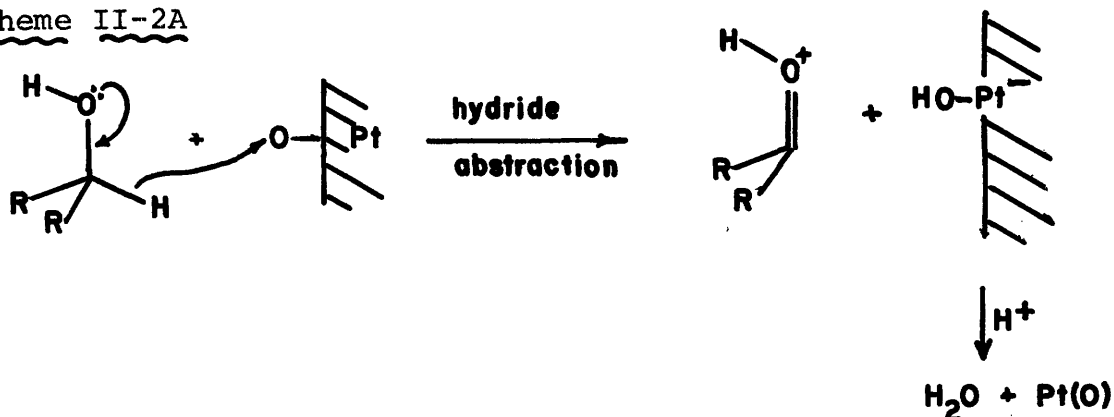
Scheme II-2B
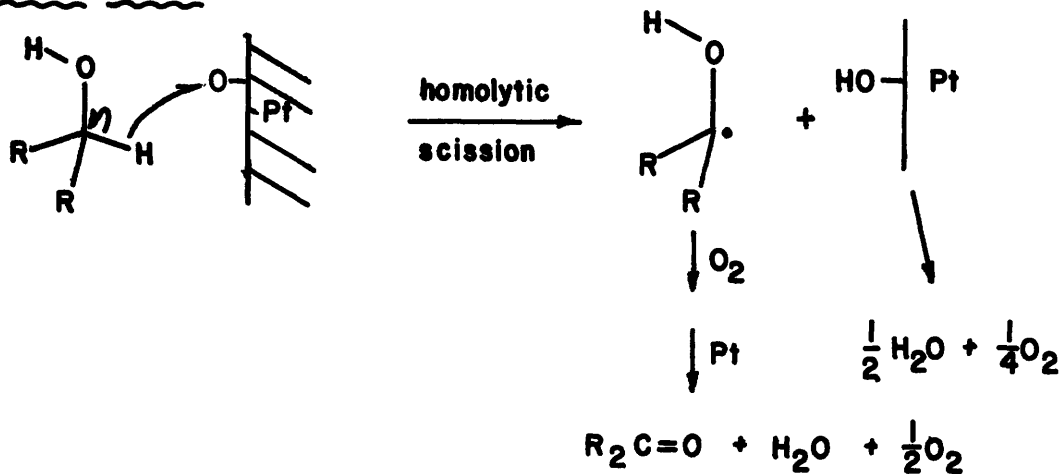
A third mechanism involves the formation of platinum
alkoxide intermediates. In this mechanism, Scheme II-3, a
platinum atom is oxidized to a Pt(II) species by molecular
oxygen. This "PtO" species is then attacked by the alcohol
to yield an intermediate hydroxyplatinum alkoxide.
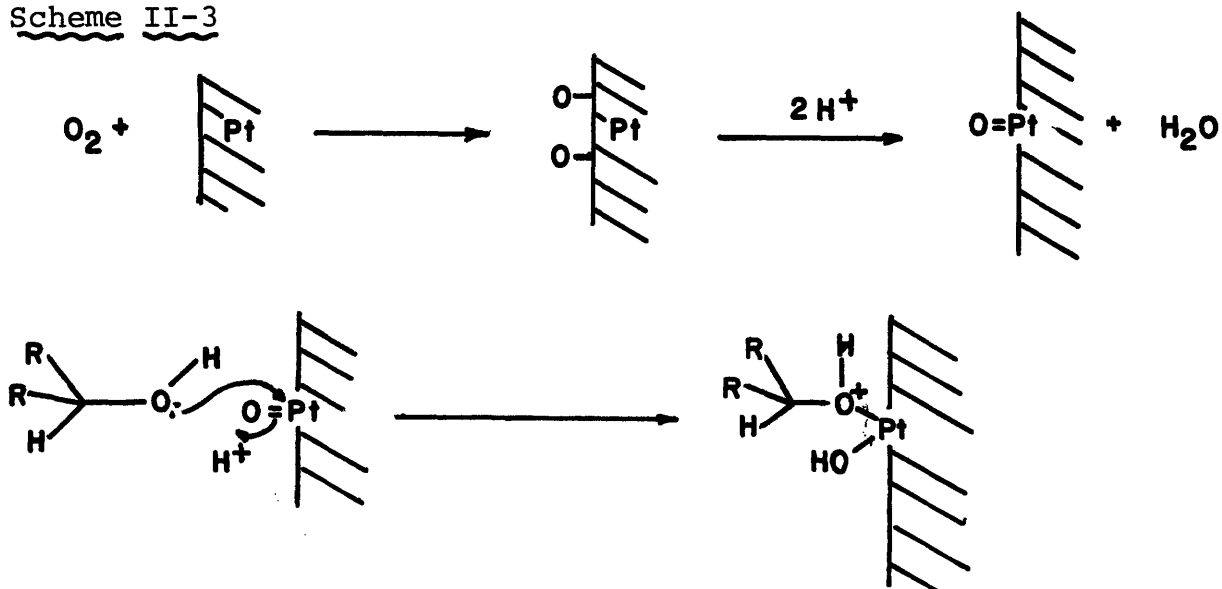
Scheme II-3

Scheme II-3A
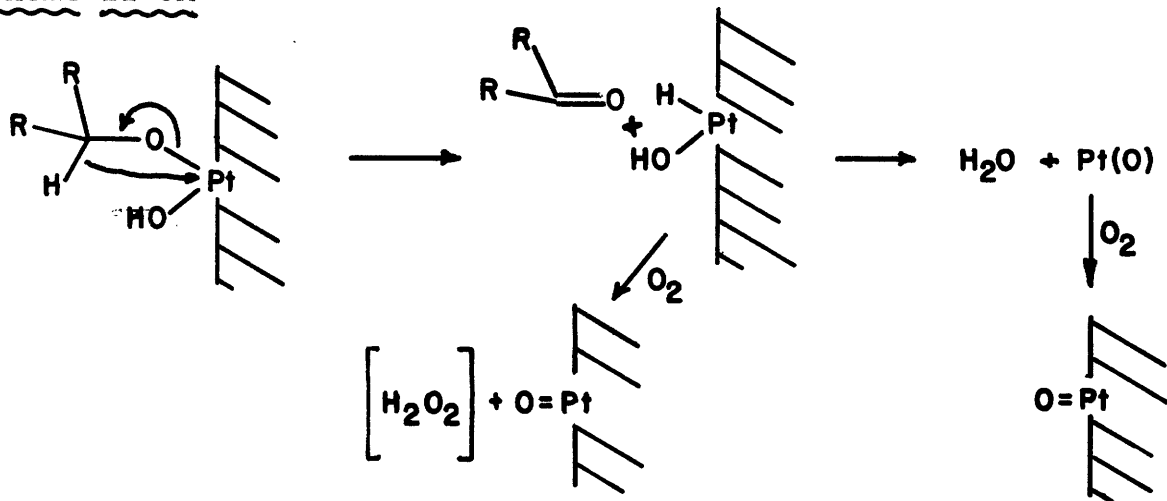
The second possibility involves loss of a proton in a manner similar to that of chromate oxidations. This possibility is outlined in Scheme II-3B.

Scheme II-3B

$$H_2O + R_2C{=}O + Pt(0)$$
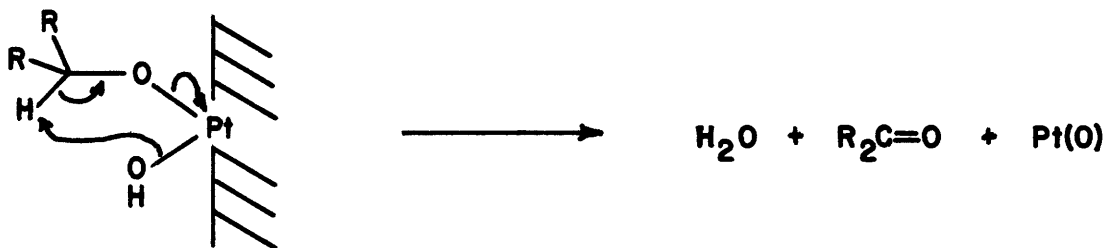
Some previous work is relevant to the mechanism of the reaction. Macrae[19] has shown the possible intermediacy of

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19) T. F. Macrae, Biochem. J., 27, 1248 (1933).

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hydrogen peroxide in the reaction of hydrogen and oxygen catalyzed by platinum black. He used an aqueous suspension of $Ce(OH)_3$ to trap hydrogen peroxide as the ceric peroxide, $Ce(OH)_3OOH$. While the yield was only 1% of theory, the quantity of ceric peroxide obtained was real in spite of problems with the system.

Müller and Schwabe[20] have measured the potential of the

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20) E. Müller, K. Schwabe, Kolloid Z., 52, 163 (1930); Chem. Abstr., 24, 5209.

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active platinum surface during the catalytic oxidation of ethanol. (Fig. II-1).

Figure II-1. Oxidation of ethanol with platinum catalyst
in aqueous NaOH.
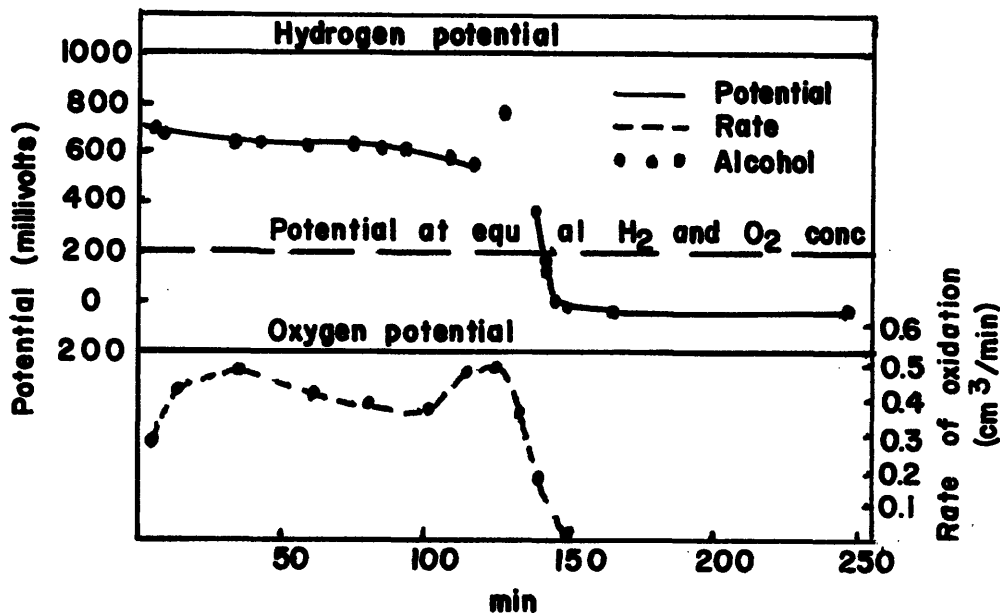
They found that during the oxidation (while O_2 uptake was observed) the potential of the platinum surface was the same as that for a platinum surface covered with hydrogen. When O_2 uptake had ceased, the potential quickly shifted to that of a platinum surface covered with oxygen.

This evidence insinuates that the "active oxygen" mechanism (Scheme II-2) is improbable since a surface covered with oxygen is necessary to promote oxidation via this mechanism. The platinum alkoxide mechanism (Scheme II-3) is not supported by the data presented above since a platinum surface covered with hydrogen is not a vital point in the

mechanism. The number of sites on the surface where platinum

alkoxides form may be small compared to the total number of

platinum atoms at the surface. The potential of the surface

would still show the same characteristics as a surface

covered with hydrogen. The evidence presented, however, is

completely consistent with the dehydrogenation mechanism.

The "active oxygen" mechanism can finally be completely

ruled out through the work of Weiland.[21a,b] He performed

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21) (a) H. Weiland, Chem. Ber., 45, 2606 (1912); (b) ibid.,
    46, 3327 (1913); (c) ibid., 45, 484 (1912); (d) ibid.,
    54, 2353 (1921).

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the oxidation of benzaldehyde and acetaldehyde over a catalytic

amount of platinum black in the presence of hydrogen acceptors

other than oxygen. The compounds Weiland used where quinone

and methylene blue. He found that in the absence of oxygen,

hydroquinone and reduced methylene blue were formed along with

benzoic acid and acetic acid. This evidence completely rules

out the necessity of an activated oxygen species derived from

molecular oxygen.

Since oxygen is not necessary in the reaction, any platinum

alkoxide mechanism which involves oxidation of a platinum(O)

species to a platinum(II) compound using molecular oxygen can be

discarded. It is doubtful that quinone or methylene blue are

capable of performing this oxidation. Therefore, the mechanism

presented in Scheme II-3B probably does not hold since

formation of platinum(O) is an integral part of the

mechanism. The mechanism in Scheme II-3A, however, is still

plausible since the oxidation of the intermediate hydroxy-

platinum hydride should occur equally facily with a number

of hydrogen acceptors. Also possible is a re-oxidation of

the intermediate hydroxyplatinum hydride to yield the

regenerated platinum(II) species and two surface-bound

hydrogen atoms. These surface-bound hydrogen atoms are then

capable of reducing any of a number of hydrogen acceptors. The

only problem which arises here is the initial oxidation to a

platinum(II) species; explained by assuming incomplete hydro-

genation of the starting platinum dioxide prior to oxidation.

While being doubtful, the complete reduction to platinum(O)

could explain the inactivation of the catalyst.

Once again the evidence that other hydrogen acceptors

than oxygen may be used is in complete accord with the dehydro-

genation mechanism.

Rocek[22] has shown that the one-electron oxidation of

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22)   (a) K. Meyer, J. Rocek, J. Am. Chem. Soc., 94, 1209
      (1972); (b) M. Doyle, R. J. Swedo, J. Rocek, J. Am.
      Chem. Soc., 95, 8352 (1973); (c) J. Rocek, A. E. Radkowsky,
      J. Am. Chem. Soc., 95, 7123 (1973).

---

cyclobutanol proceeds via a different pathway than the two-

electron oxidation. One-electron oxidants react with

cyclobutanol to form ring-opened products.[22a] Oxidants

investigated in this category include cerium(IV), manganese

(III) and vanadium(V). The reaction involved is shown in

Scheme II-4.

Scheme II-4.
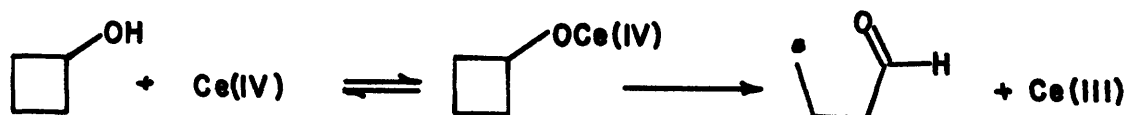
No cyclobutanone is observed in the product mixture resulting

from a one-electron oxidation and, in addition, the reactivity

of cyclobutanol toward a one electron oxidant is more than

1000 times greater than that of cyclopentanol toward the same

oxidant. In all cases tried, the smallest rate difference

found between cyclobutanol and a secondary alcohol, isopropanol,

toward one-electron oxidant, Cr(IV), was a factor of 20 greater

for cyclobutanol.[23]

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23) M. Rahman, J. Rocek, J. Am. Chem. Soc., 93, 5455 (1971).

_____

In contrast, two-electron oxidants react with cyclobutanol

to give only cyclobutanone as the product.[22b] (Scheme II-5.)

Scheme II-5.

When the relative rates of oxidation of cyclobutanol and cyclopentanol toward a two-electron oxidant, Cr(VI), were determined, it was found that cyclobutanol was oxidized only 1.08 times faster than cyclopentanol.[22a]

The oxidation of cyclobutanol and cyclopentanol with platinum black catalyst has been investigated. First, only cyclobutanone and unreacted cyclobutanol were present after oxidation; no ring opened products were detected. Second, the relative reactivities cyclobutanol and cyclopentanol were determined and it was found that cyclobutanol was oxidized only 3.8 times faster than cyclopentanol. (Table II-1.)

Table II-1. Relative rates of oxidation of cyclic alcohols with Adams' catalyst and molecular oxygen.
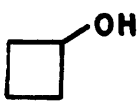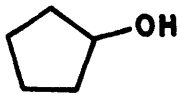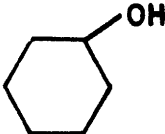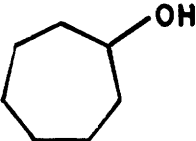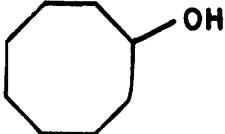
Alcohol	Rate/Rate$_{cyclohexanol}$
	4.9
	1.3

Table II-I. (cont.)

This evidence points to a two-electron oxidation step in the platinum-catalyzed oxidation. In terms of the dehydrogenation mechanism previously proposed (Scheme II-1) the loss of a hydrogen radical from oxygen can be ruled out. This process should lead to ring-opened products and greatly accelerated rates. The loss of hydride from the α-carbon atom however, is a two-electron process and this mechanism, Scheme II-1B fits the cyclobutanol oxidation data perfectly. The 1,3-hydride shift of an intermediate hydroxyplatinum alkoxide, Scheme II-3A is also in accord with the cyclobutanol oxidation results.

Additional evidence can be presented against the loss of a hydrogen atom. Oxidation via loss of a hydrogen radical in a one-electron process should form an intermediate peroxide in the presence of oxygen (Scheme II-6).

Scheme II-6.
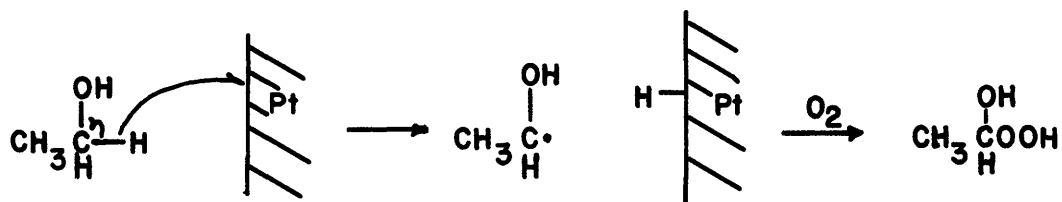
Rottenberg[24] has shown that when [18]O_2 is used as the

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24) (a) M. Rottenberg, M. Thurkauf, _Helv. Chim. Acta_, _42_, 226 (1959); (b) M. Rottenberg, P. Baertschi, _Helv. Chim. Acta_, _39_, 1973 (1956).

_____
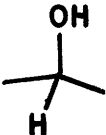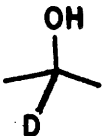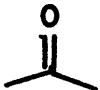
oxidizing agent, no heavy oxygen is incorporated into the product. In the case of ethanol, the intermediate hydroxyperoxide should decompose to yield hydrogen peroxide and acetaldehyde with all of the oxygen-18 present in the hydrogen peroxide. However, this intermediate peroxide may also attack another acetaldehyde molecule. Decomposition of the resulting peroxy compound should lead to acetic acid labelled with oxygen-18 in 50% of the oxygens.[24a] (Scheme II-7.)

Scheme II-7.
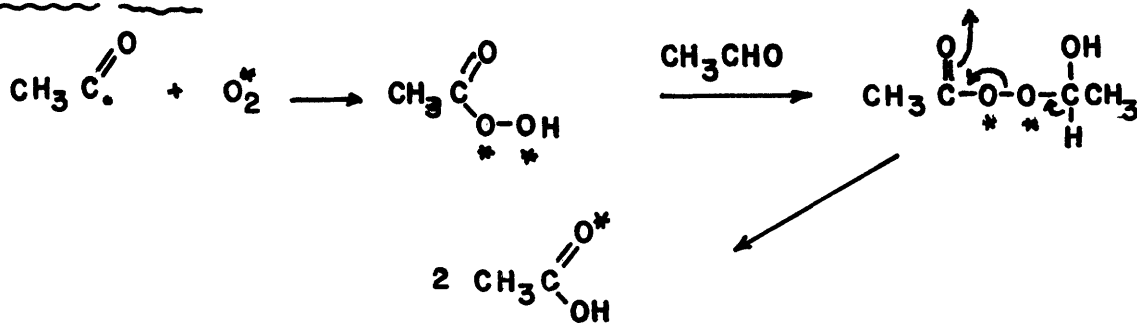
Additional support for the loss of hydride comes from the deuterium isotope effect. The deuterium isotope effect for the oxidaiton of isopropanol with platinum and molecular oxygen has been determined using proton nmr to determine the amounts of each alcohol present. The experimental data are presented in table II-II.

Table II-II. Oxidation of propanol-2 and 2-propanol-2-d_1 with Adams' catalyst in water.

Compound	mmoles present[a]	
	Start	Finish
OH structure with H	1.11	0.57
OH structure with D	1.00	0.71
O structure	0.00	0.82[b]

(a) Determined by nmr. (b) The reaction went to 40.6% of completion.

Since k_H/k_D is small and the reaction was stopped at only 40% completion, the approximation can be made that[25]

$$\frac{\text{OH oxidized}}{\text{OH (D) oxidized}} = \frac{k_H}{k_D} \qquad \frac{0.54}{0.29} = 1.9.$$

25) L. Melanger, "Isotope Effects on Reaction Rates,"
Ronald Press Co., New York, N. Y., 1960.

This number is probably only accurate to ±20% (0.4) since

the concentration of all species was measured by nmr integration.

Deuterium isotope effects have been measured for other

reactions which are known to proceed via a rate-limiting

hydride transfer.[26]

26) (a) R. Stewart, "Oxidation Mechanisms," W. A. Benjamin,
Inc., New York, N. Y., 1964, p. 18; (b) W. A. Waters,
"Mechanism of Oxidation of Organic Compounds," John
Wiley and Sons, Inc., New York, N. Y., 1964, p. 67;
(c) E. S. Lewis, M. C. R. Symons, Quart. Rev., 12, 230
(1958); (d) N. C. Deno, H. J. Peterson, G. S. Saines,
Chem. Rev., 60, 7 (1960); (e) F. H. Westheimer, Chem. Rev.,
61, 265 (1961).

Wiberg[27] has reported a deuterium isotope effect of

27) K. B. Wiberg, J. Am. Chem. Soc., 76, 5371 (1954).

1.8 for the Cannizzaro reaction, a reaction which most likely

involves hydride transfer in the rate limiting step. Bartlett

and McCollum[28] have shown that k_H/k_D for the oxidation of

28) P. D. Bartlett and J. D. McCollum, J. Am. Chem. Soc., 78,
1441 (1956).

isopropanol by triphenylmethyl carbonium ion ranges from

1.8 to 2.6. Galton and Abbas[29] have reported a deuterium

29) S. A. Galton, R. Abbas, J. Org. Chem., 38, 2008 (1973).

isotope effect for a Clemmensen reduction of 1.53. Several

other reports of deuterium isotope effects of 1.8-2.6 for

hydride transfer reactions can also be found in the literature.[30-32]

30) M. F. Hawthorne, E. S. Lewis, J. Am. Chem. Soc., 80, 4296 (1958).

31) L. Kaplan, J. Am. Chem. Soc., 80, 2639 (1958).

32) G. Baddely, W. Pickles, J. Chem. Soc., 3726 (1953).

Swain[33] has determined the deuterium isotope effect for

33) C. G. Swain, R. A. Wiles, R. F. W. Bader, J. Am. Chem. Soc., 53, 1945 (1961).

the oxidation of isopropanol with bromine to be 2.9 and

explained the relatively small isotope effect is in keeping

with a rate-determining hydride loss. He also observed an

-OD deuterium isotope effect of 1.5. This value is much too

low for a proton transfer in the rate determining step; the

smallest value for the isotope effect should not be less than

2.8, even if the proton were almost completely transferred in

the transition state.[26e,33,34]

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34) (a) F. H. Westheimer, Y. W. Chang, J. Am. Chem. Soc., 63, 438 (1959); (b) F. H. Westheimer, J. Am. Chem. Soc., 80, 3030 (1958) and references therein.

Westheimer[26e,34-36] has shown the mechanism for oxidation

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35) F. H. Westheimer, Chem. Rev., 45, 419 (1949).

36) F. H. Westheimer, N. Nicolaides, J. Am. Chem. Soc., 71, 25 (1949).

---

of isopropanol by chromate to involve esterification

as the initial step (Scheme II-8).

Scheme II-8.
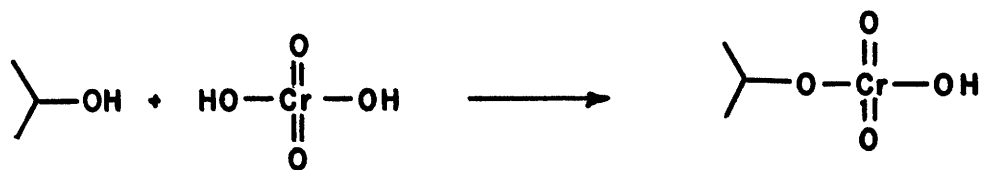
This intermediate chromate ester is a metal alkoxide.

The oxidation occurs through loss of an α-proton by either a

cyclic or base assisted mechanism. (Scheme II-9.)

Scheme II-9.
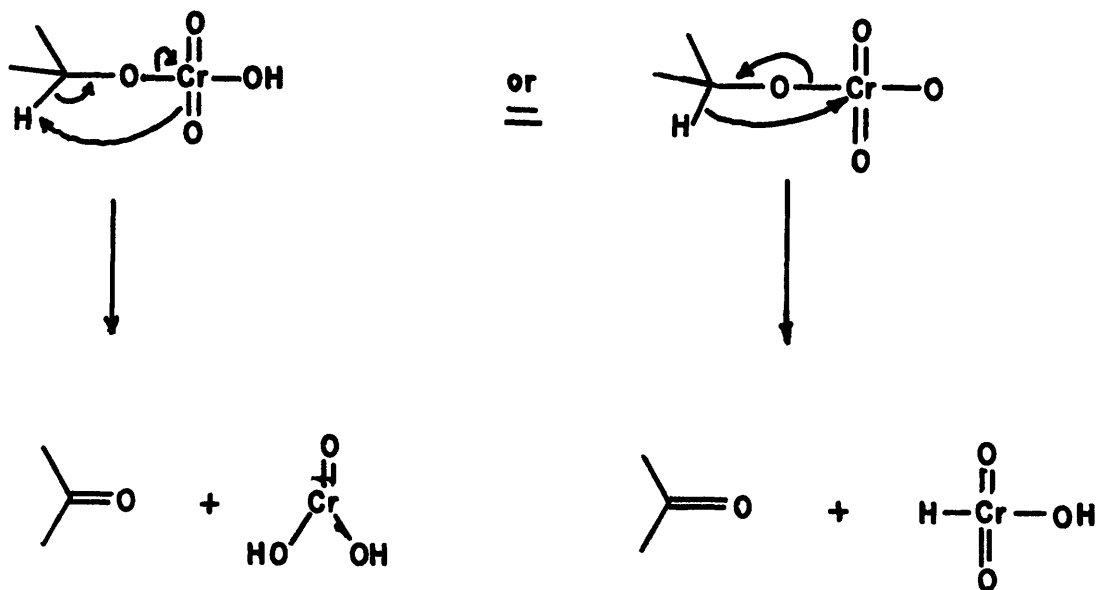
The deuterium isotope effect for the oxidation of alcohols by a Cr(VI) species is large, approx 6-9.[26e,35] If the oxidation of an alcohol by molecular oxygen over a platinum catalyst proceeds through a metal alkoxide in a manner similar to the Cr(VI) oxidation of alcohols then the observed deuterium isotope effect of 1.9 is inconsistent with the mechanism proposed in Scheme II-3B.

The alternate possibility is the 1,3-hydride shift as presented in Scheme II-3A. In general, kinetic isotope effects have been shown to be of magnitude 1.5-2.9 in inter-molecular hydride transfers only. Intramolecular hydride shifts are only very poorly documented.[37]

37) G. J. Karabatsos, C. E. Orzech, J. Am. Chem. Soc., 84,
2838 (1962).

Of course, the loss of hydride in Scheme II-1B of the
dehydrogenation mechanism still fits the experimental data.

Our experiments with the oxidation of 4-t-butylcyclohex-
anol have shown that loss of hydride in the rate-determining
step is irreversible. Oxidation of cis- and trans-4-t-butyl-
cyclohexanol yields only starting material and 4-t-butylcyclo-
hexanone. (Scheme II-10.)

Scheme II-10.
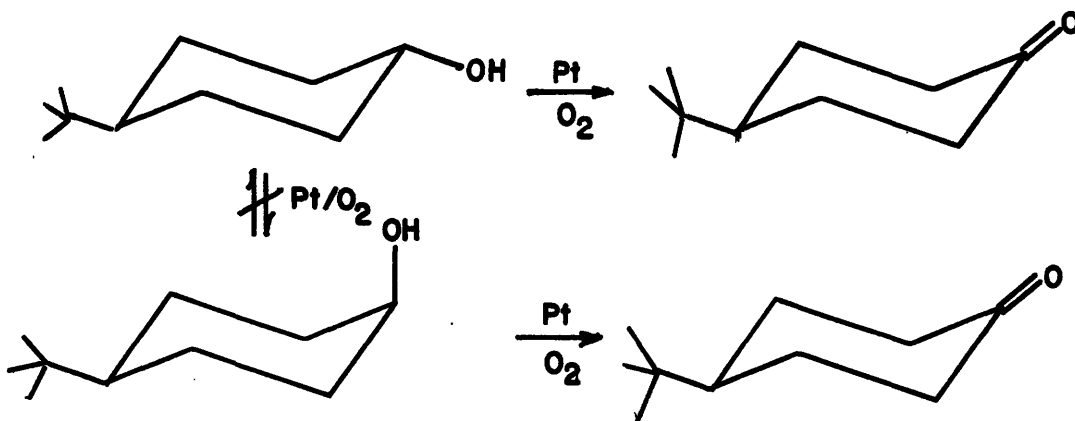
No isomerization of diastereomers could be detected by glpc.
Hydride loss is generally irreversible and in this case,
reversibility of the loss of hydride should result in isomeriza-

tion of the cis-isomer to give the thermodynamically more
stable trans-isomer. (Scheme II-11.)

Scheme II-11.
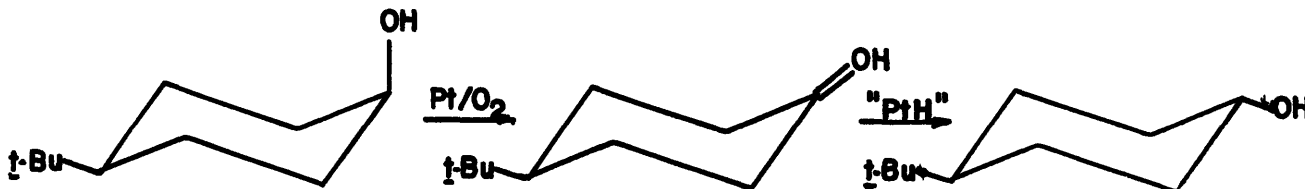
Our experiments with the oxidation of 4-t-butylcyclohexanol
also show that the stereochemical requirements for the oxida-
tion are similar to those for the hydrogenation of 4-t-butyl-
cyclohexanone as predicted by the von Auwers-Skita rule.
The von Auwers-Skita rule[38-41] states simply that in neutral

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38) R. J. Wicker, J. Chem. Soc., 2165 (1956).

39) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin,
    Inc., Menlo Park, Calif., 1972, p. 26.

40) S. Mitsui, et al., Tetrahedron, 29, 1531 (1973).

41) J. H. Brewster, J. Am. Chem. Soc., 76. 6361 (1954).

---

or basic media, hydrogenation of cyclohexanone will provide
predominantly equatorial alcohols while hydrogenation in
acidic media will produce primarily axial alcohols.

Figure II-1 shows that in acidic media, the axial alcohol,
cis-4-t-butylcyclohexanol, is oxidized much more rapidly than

the equatorial alcohol, trans-4-t-butylcyclohexanol. This

preferential oxidation is the expected result if the reaction

is similar to a dehydrogenation mechanism. In a neutral

medium, which usually shows the same von Auwers-Skita trends

as basic media[42] the axial alcohol is still oxidized faster

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42) D. H. R. Barton, J. Chem. Soc., 1027 (1953).

---

than the equatorial but the relative rates have changed

drastically. (Figure II-2.) The axial alcohol is oxidized

2.7 times faster than the equatorial in neutral benzene while

in acidic benzene, during the early stages of the reaction,

the axial alcohol is oxidized about 9 times faster.

Brewster[41] has discussed the mechanism of the hydrogena-

tion of cyclohexanones over both noble metal catalysts and

active metals. He concludes that catalytic hydrogenation of

cyclohexanones occurs via a hydride transfer from a metal-

hydride to the ketone. The resulting alkoxide then picks up

a proton from the solvent. The bulky metal surface transfers

a hydride to the less hindered side of the molecule which

results in axial alcohols. A dehydrogenation mechanism

(Scheme II-1B) which invokes the loss of hydride to the metal

surface to form a metal hydride would account for the observed

preferential oxidation of axial alcohols; the equatorial

hydrogen is more readily available for hydride abstraction in

Figure II-2. Oxidation of 4-t-butylcyclohexanol in acidic (p-toluenesulfonic acid) benzene.
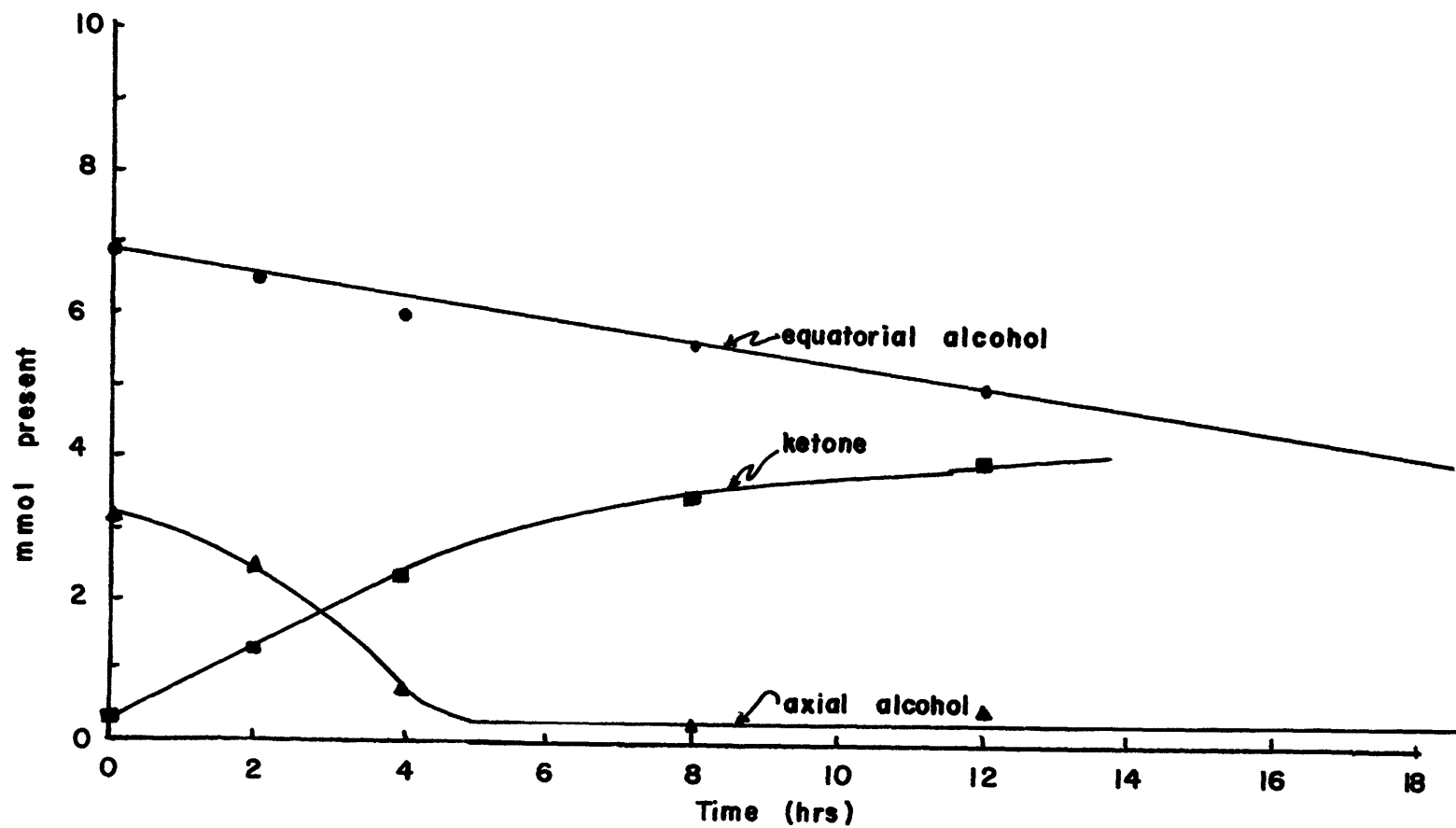
Figure II-3.   Oxidation of 4-t-butylcyclohexanol in neutral benzene.
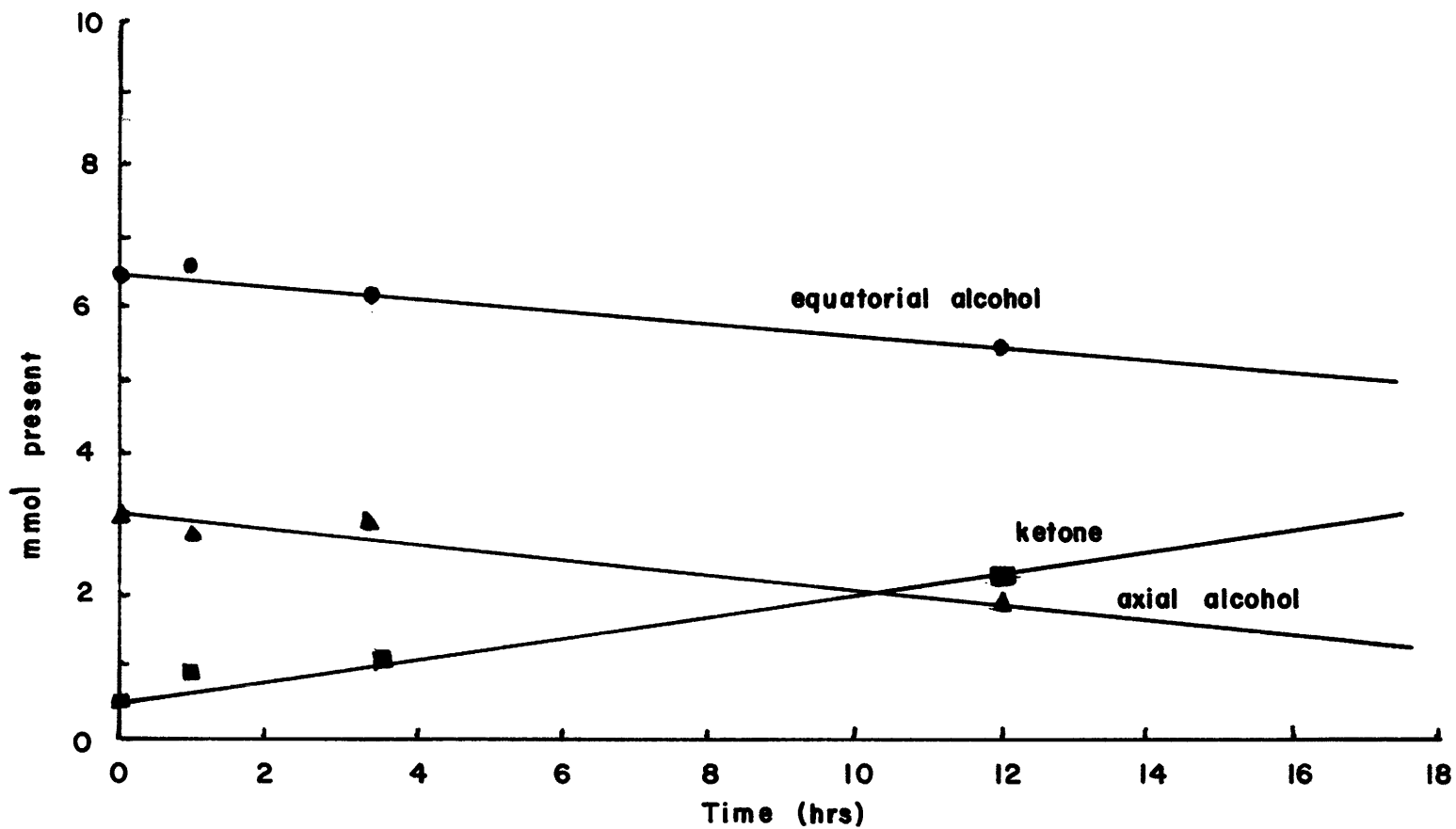
the axial alcohols.

The formation of a platinum alkoxide however, should (a) show very little preference for axial alkoxide formation over equatorial alkoxide and (b) show a preference for equatorial alkoxide formation if hindrance plays any part in the reaction - not the observed result. Brewster states that the reduction of cyclohexanones with an active metal surface, a surface in which alkoxides are formed as intermediates, the equatorial alcohol predominates.

Since platinum alkoxide formation bears some resemblance to the formation of chromate esters, the relative rates for the oxidation of axial and equatorial alcohols in this manner should be similar to the relative rates for chromate oxidation. Kwart[43] has shown that cis-4-t-butylcyclohexanol is oxidized

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43) H. Kwart, Chem. Ind., (London), 610 (1962).

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only 1.46 times faster than trans-4-t-butylcyclohexanol with chromic acid.

A final point of support for both the dehydrogenation mechanism and the platinum alkoxide mechanism lies in the relative rates of oxidation in acidic and basic media. In acidic media the reaction proceeds much more slowly than in basic media.[1] This difference can be explained by protonation or deprotonation of the alcohol simultaneous to abstraction of of hydride. (Scheme II-12.)

Scheme II-12.

Acid media
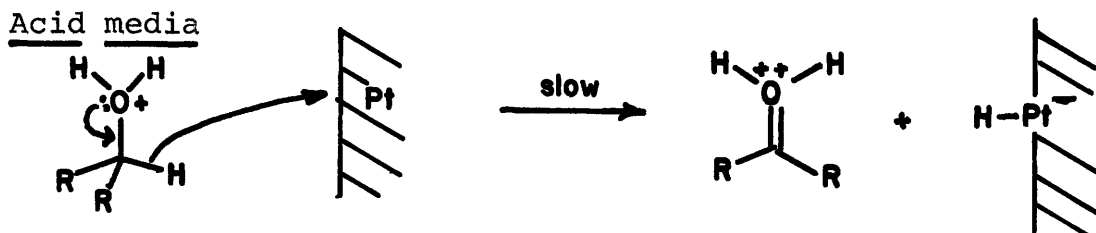
Scheme II-13.
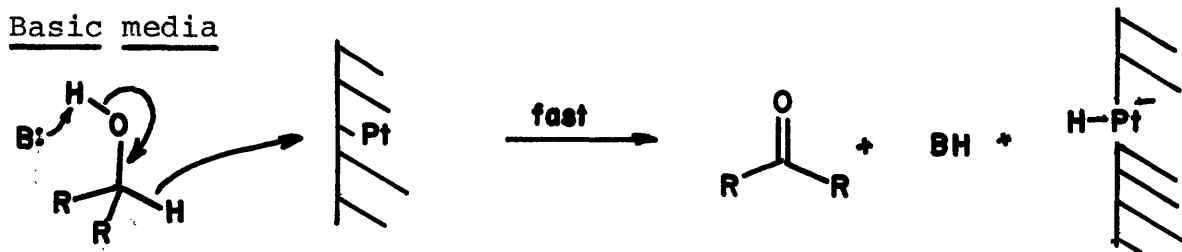
Basic media

In acid media hydride abstraction is slowed due to development of a positive charge on the alcohol oxygen. In basic media however, the base can accelerate the reaction by removing the alcohol proton as the hydride is being abstracted.

Conclusions. The dehydrogenation mechanism presented in Scheme I-1B gives the closest approximation to the mechanism of oxidation by Adams' catalyst. The rate determining step involves an irreversible loss of hydride to the active catalyst surface. The species which loses hydride is undoubtedly adsorbed on the catalyst surface; these considerations have been omitted for simplicity. A hydrogen acceptor, not necessarily oxygen, is needed to remove the adsorbed hydrogen from the surface and complete the catalytic cycle.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined on a Perkin-Elmer R-20B spectrophotometer or on a Varian T-60 spectrophotometer. Glpc analyses were performed on a Perkin-Elmer model 990 gas chromatograph. Platinum dioxide was purchased from Englehard Industries. 4-t-Butylcyclohexanol, 4-t-butylcyclohexanone, cyclobutanol, cyclopentanol, cyclo-hexanol, cycloheptanol and cyclooctanol were purchased from the Aldrich Chemical Co. and used without further purification. Acetone was distilled from Linde 3 A molecular sieve on a 10 cm spinning band (stainless steel) column before use.

Preparation of the Catalyst. (Typical Procedure A.)
Platinum dioxide (0.23 g, 1.0 mmol) was hydrogenated for 15 min at 45 psi of hydrogen in 10 ml of water using a Parr hydrogenation apparatus. The vessel was evacuated and flushed with air several times before opening. The catalyst was transferred wet and used immediately after preparation.

Preparation of the Catalyst (Typical Procedure B.)
Platinum dioxide (0.23 g, 1.0 mmol) was placed in a 100 ml, round-bottomed flask equipped with a Teflon-coated magnetic stirring bar and No-air stopper. A vigorous stream of nitrogen was bubbled through the mixture for 15 min with stirring to flush out all oxygen present. A vigorous stream

of hydrogen was then passed through the mixture for 15 min
followed by a vigorous stream of nitrogen for an additional
15 min. Catalysts prepared by either procedure A or B had
approximately the same activity.

Competitive Oxidation of Cyclobutanol and Cyclopentanol.
(Typical Procedure.) Platinum black (0.5 mmol) was prepared
as described previously (procedure A) except that 25 ml of
pentane was used as the solvent. Nonane (100 µl, internal
standard), cyclobutanol (0.180 g, 0.200 ml, 2.50 mmol) and
cyclopentanol (0.215 g, 0.227 ml, 2.50 mmol) were added to
the catalyst suspension. A Teflon-coated stirring bar was
placed in the flask and the mixture was stirred vigorously
under a slight positive pressure of oxygen for 24 hr.
Aliquots were taken at regular intervals and analyzed by glpc.
The relative rates of oxidation were determined at various
intervals early in the reaction.

2-Propanol-2-d_1. Acetone (2.32 g, 40.0 mmol) in 10 ml
of dry ether was added dropwise to a stirred solution of
lithium aluminum deuteride (0.42 g, 10.0 mmol) in 20 ml of
ether. The mixture was stirred at reflux for 2 hr. The
mixture was then hydrolyzed by the consecutive addition of
0.42 ml of water, 0.42 ml of 15% aqueous sodium hydroxide and
1.3 ml of water. The mixture was dried over Linde 3 A molecular
sieves and filtered. Distillation afforded 1.6 g (70%) of
2-propanol-2-d_1. The product was found to contain 15% water

by nmr. No isopropanol or acetone was detected.

Competitive Oxidation of Isopropanol and 2-Propanol-2-d_1 with Adams' Catalyst. Platinum black catalyst (0.195 g, 1.00 mmol) prepared as previously described in procedure A, was placed in a 25 ml round bottomed flask equipped with a No-air stopper and a Teflon-coated magnetic stirring bar. The flask was flushed with oxygen with vigorous stirring. Isopropanol (0.15 g, 2.5 mmol) and 2-propanol-2-d_1 (0.15 g, 2.5 mmol) were added via hypodermic syringe and the reaction mixture stirred vigorously under a positive pressure of oxygen. Oxygen uptake measured by gas buret. Aliquots were taken at intervals and analyzed by nmr.

A Perkin-Elmer R-20B nuclear magnetic resonance spectrophotometer was used for these analyses. It was possible to obtain baseline resolution for the propanol-2 methyl doublet (J=6 Hz) and the 2-deuteropropanol-2 methyl triplet (J=0.8 Hz) situated between the peaks of the undeuterated methyl doublet.

Trans-4-t-butylcyclohexanol. Trans-4-t-butylcyclohexanol was prepared via a published procedure.[47]

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47) E. L. Eliel, J. L. Martin, D. Nasipuri, Org. Syn.,
     Coll. Vol. V., 175 (1973).

Separation of cis from trans-4-t-butylcyclohexanol. A mixture of cis- and trans-4-t-butylcyclohexanol (5.0 g, 65% trans) was dissolved in 500 ml of pentane. The solution

was added to 500 g of anhydrous calcium chloride and stirred

vigorously for 4 hr. The mixture was filtered and the

pentane layer was found to contain 3.0 g of alcohol which was

enriched in cis isomer (55% cis). An additional 100 g of

anhydrous calcium chloride was stirred vigorously for several

hr in 250 ml of pentane until a fine powder resulted.

Alumina (110 g, Woelm, Activity IV) was added and the mixture

was stirred well and poured into a chromatography column.

The enriched alcohol from above was placed on the column and

eluted with 5% ethyl acetate in hexane to yield 0.35 g of

cis-4-t-butylcyclohexanol, mp 76-8°, containing about 10%

4-t-butylcyclohexanone as determined by glpc.[47]

Competitive Oxidation of cis- and trans-4-t-butylcyclo-

hexanol in Acid Medium with Adams' Catalyst. (Typical

Procedure.) Platinum black (0.195 g, 1.00 mmol) was prepared

as previously described in 50 ml of benzene. 4-t-Butylcyclo-

hexanol (1.56 g, 10.0 mmol) and p-toluenesulfonic acid (0.085 g,

0.50 mmol, 0.01N solution) was added and the mixture stirred

vigorously under a positive pressure of oxygen for 24 hr.

Aliquots were taken at various intervals and analyzed by

glpc using internal standard techniques (n-tetradecane). Other

oxidations of 4-t-butylcyclohexanol were done in an analogous

manner.

Part III.

Selectivity in Organic Group Transfer in Reactions

of Mixed Lithium Diorgano cuprates.

This work has been published: W. Harry Mandeville

and George M. Whitesides, J. Org. Chem., 39, 400 (1974).

Appendix

The Attempted Synthesis of Biotin.

Biotin (29) has been synthesized many times previously[1]

29

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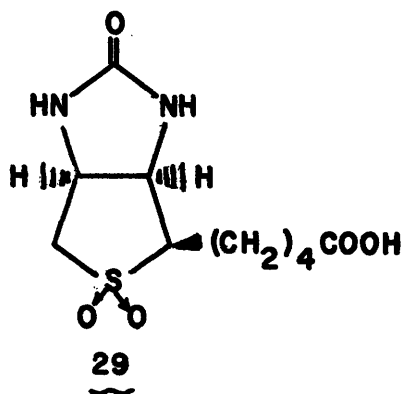
1) (a) See E. E. Reid, "Organic Chemistry of Bivalent Sulfur,"
   Vol. III, Chemical Publishing Co., New York, N. Y., 1960,
   p. 25. For a good review of biotin chemistry see Ann. Rev.
   Biochem., each year for a brief report of the year's progress;
   v. du Vigneaud, K. Hoffman, D. B. Melville, J. R. Rachelle,
   J. Biol. Chem., 140, 763 (1941); (c) S. A. Harris, D. E.
   Wolf, R. Mozingo, K. Folkers, Science, 97, 447 (1943);
   S. A. Harris, N. R. Easton, D. Heyl, A. N. Wilson, K.
   Folkers, J. Am. Chem. Soc., 66, 1756 (1944); S. A. Harris,
   D. E. Wolf, R. Mozingo, G. E. Arth, R. C. Anderson,
   N. R. Easton, K. Folkers, ibid., 67, 2096 (1945); (d)
   G. W. Kilmer, H. McKennis, J. Biol. Chem., 152, 103 (1944);
   (e) A. Grussner, J. P. Borquin, O. Schnider, Helv. Chim.
   Acta, 28, 517 (1945); 29, 770 (1946); (f) L. C. Cheney,
   J. R. Piening, J. Am. Chem. Soc., 67, 2252 (1945); U. S.
   Patent 2,466,004 (1949); Chem. Abstr., 44, 3532 (1950);
   (g) L. C. Cheney, U. S. Patent 2,052,422 (1950); Chem.
   Abstr., 44, 6440 (1950); (h) B. R. Baker, et al.,
   J. Org. Chem., 12, 138, 155, 160, 167, 174, 186, 322,328,
   475, 483 (1947); 13, 123 (1948); (i) C. A. Grob, H. von
   Sprecher, Helv. Chim. Acta, 35, 885 (1952); (j) T. Taguchi,
   Y. Sato, K. Watanabe, T. Mukaiyama, Chem. Letters, 729 (1974).

since the first correct proof of its structure by du Vigneaud.[2]

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2) K. Hofmann, D. B. Melville, V. du Vigneaud, J. Biol. Chem.,
    141, 207 (1941); 144, 513 (1942); V. du Vigneaud, D. B.
    Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C.
    Keresztezy, S. A. Harris, ibid., 146, 475 (1942). See
    also R. Lett, A. Marquett, Comptes rend. Ser. C, 268, 2348
    (1969) for the nmr spectra of biotin and its analogs and
    J. Trotter, J. A. Hamilton, Biochemistry, 5, 713 (1966)
    for the x-ray crystal structure determination of biotin.

Even the simplest of these syntheses, the one currently used

in the commercial process[3] is long and tedious. The goal

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3) M. W. Goldberg, L. H. Sternbach, U. S. Patent 2,489,232
    (1949); Chem. Abstr., 45, 184 (1951).

---

of this project was to design a simple, practical synthesis

of biotin.

The first route attempted was via the sulfolene inter-

mediate 1,3-diacetyl-4H,6H-thiopheno[d]imidazolone-5,5-

dioxide (30). This sulfolene was synthesized from the

30
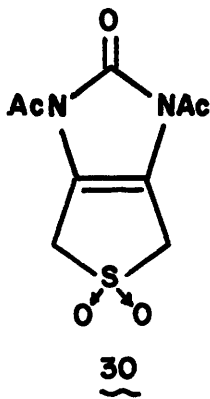
corresponding bis(exodiene), 33, as shown in Scheme A-1.

Except for the C_5 sidechain, this compound possesses correct

Scheme A-1.
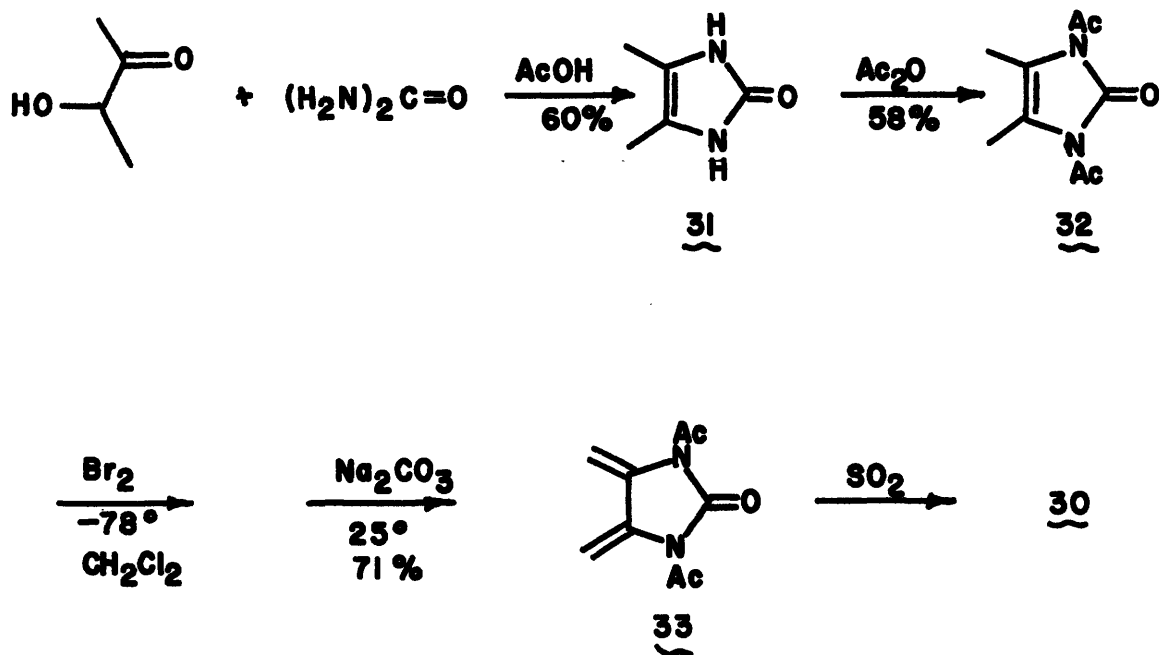
backbone for biotin. A typical reaction sequence involved

refluxing 3-hydroxy-2-butanone (acetoin) and urea in 20%

aqueous acetic acid to make 4,5-dimethylimidazolone (31) as

described by Biltz[4] followed by acetylation with acetic

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4) H. Biltz, Chem. Ber., 40, 4799 (1907).

_____

anhydride to yield the 1,3-diacetyl-4,5-dimethylbenzimidazolone,

(32).[4] Bromination of 32 at -78° in methylene chloride followed

by a thermal elimination at 25° in the presence of sodium

carbonate yielded 1,3-diacetyl-4,5-bis(exomethylene)imidazolone

(33) in good yield. Treatment of 33 with sulfur dioxide at

25° in acetone yielded 30 in 71% yield.

The next step in the proposed synthesis was the alkyla-

tion of the sulfolene derivative in order to introduce the

C_5 carboxylic acid side-chain. This process was attempted

with methyl ω-halo valerates, 34, and a variety of bases

Scheme A-2.

30 + X(CH₂)₄CO₂CH₃ —base→//— 35

34a, X = Br
34b, X = I
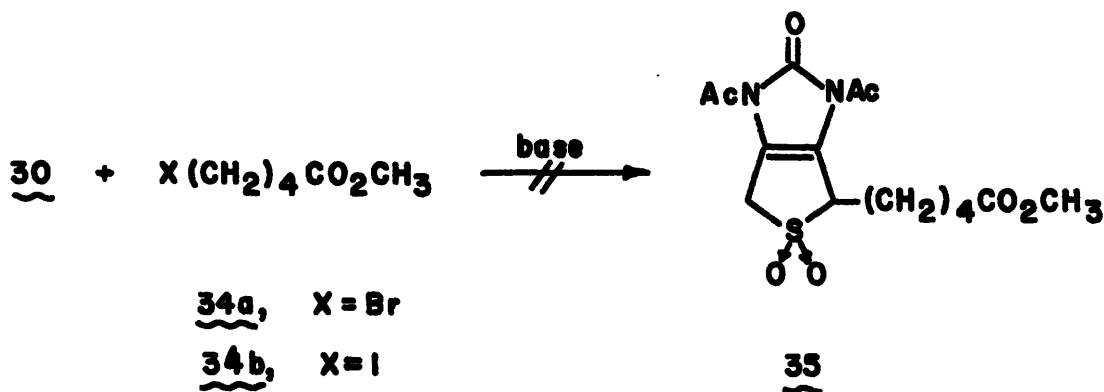
(Scheme A-2): potassium hydride in DMF, potassium t-butoxide

in DMSO and lithium di-iso-propylamide in THF. None of these

systems proved successful. Attempts at deacylation of the

imidazolone nitrogens prior to alkylation resulted in decompo-

sition. In addition, unacylated imidazolones are very

difficult to work with due to their insolubility in most

common solvents.

After the alkylation of 30 had failed it was decided
that the imidazolone precursor could be synthesized with the
side-chain already attached. The proposed route to 4-methyl-
imidazolone-5-ω-hexanoic acid (38) is shown in Scheme A-3.

36 → 37a, X = OH   37b, X = halogen   37c X = NH₂ → 38
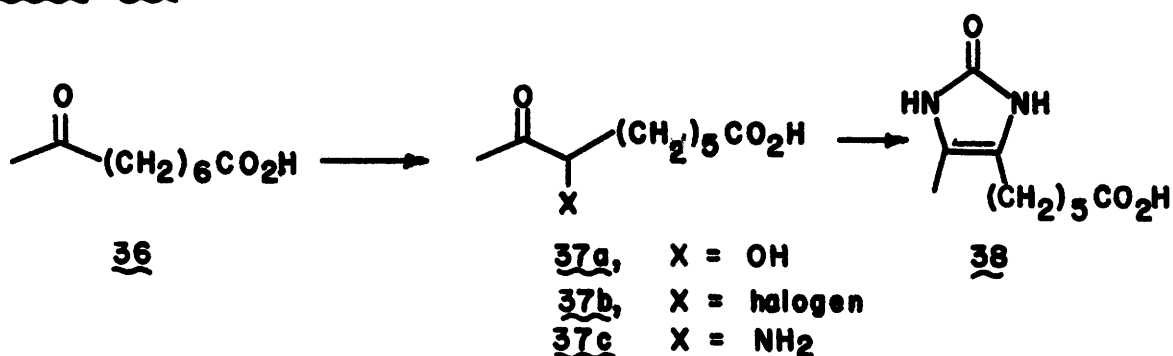
8-Ketononanoic acid (36) was prepared using the method
of Gaubert, Linstead and Rydon.[5] Of the three 8-ketononanoic

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5) P. Gaubert, R. L. Linstead, H. N. Rydon, *J. Chem. Soc.*,
    1974 (1937).

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acids functionalized in the 7-position only one has been
synthesized, 37c. It was prepared *via* hydrogenation of the
7-oximo-8-ketononanoic acid (39) which was made from the
reaction of ethyl nitrite with 36. (Scheme A-4.)

Scheme A-4.

36 $\xrightarrow[\text{60\%}]{\text{EtONO}}$ 39 $\xrightarrow{\text{H}_2}$ 37c
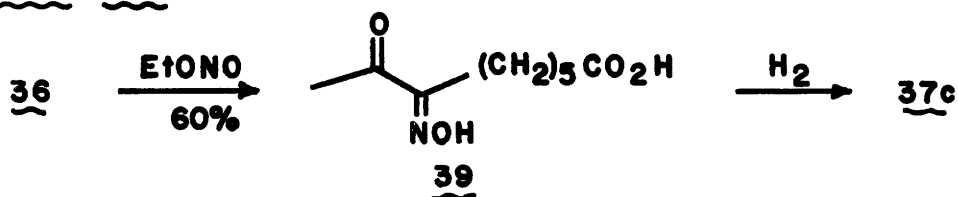
Compound 37c 7-amino-8-ketononanoic acid, did not condense as expected with iso-cyanic acid, prepared from urea, however. (Scheme A-5.)

Scheme A-5.

$$\textbf{37c} \quad \xrightarrow[]{\textbf{HN=C=O}} \!\!\!\!/\!\!/\!\!\!\!\longrightarrow \quad \textbf{38}$$
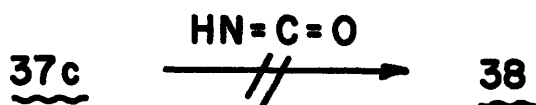
α-Bromoketones are readily prepared[6] and imidazolones

6) P. Z. Bedoukian, J. Am. Chem. Soc., 67, 1430 (1945); see also H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., 1972, p. 459.

similar to 38 have been prepared from the α-halo ketones.[7]

7) T. Taguchi, Y. Sato, K. Watanabe, T. Mukaiyama, Chem. Letters, 401 (1974).

This route seems to be the next most reasonable in this synthesis.

Conclusions. While we have not yet prepared biotin, the groundwork has been established for the construction of its bicyclic ring system. Major hurdles to be overcome include stereospecific hydrogenation of the imidazolone

4,5-double bond and reduction of the sulfone moiety to the

sulfide. An alternative to the later may be direct addition

of H_2S to the bis-(exodiene), 33.

Experimental Section

General. See experimental section, Part I.

4,5-Dimethylimidazolone (31). 4,5-Dimethylimidazolone was prepared in a variation of the method of Biltz.[4] 3-Hydroxy-2-butanone (170 g, 1.93 mol) and urea (400 g, 6.67 mol) were refluxed in 450 ml of 20% aqueous acetic acid for 4 hr. The mixture was cooled to 5° and filtered. The solid thus obtained was washed with 500 ml of water, 500 ml of 95% ethanol and finally with 500 ml of ether. Drying yielded 130 g of product with mp >320° (lit.[27] 345-5°); yield 60%.

1,3-Diacetyl-4,5-imidazolone (32). 1,3-Diacetyl-4,5-imidazolone was prepared via the method of Biltz.[4] 4,5-Dimethylimidazolone (31) (140 g, 1.25 mol) and sodium acetate (280 g) were refluxed in 1200 g of acetic anhydride for 1.5 hr. The mixture cautiously hydrolyzed with 800 ml of water and cooled to 5°. Filtration afforded 142 g, 58%, of 32. The compound was recrystallized from ethanol to mp 106.5-8.5° (lit.[27] 117-8) and nmr (CDCl$_3$) δ 2.23 (s, 3), 2.64 (s, 3).

1,3-Diacetyl-4,5-bis(exo-methylene)imidazolone (33). A solution of 32 (44.4 g, 0.225 mol) in 600 ml of methylene chloride was cooled to -78° in a Dry-Ice/acetone bath. Bromine (36.8 g, 0.23 mol, 12.6 ml) in 100 ml of methylene chloride was added dropwise with stirring. After the addition was complete, finely powdered, anhydrous sodium carbonate

(95.6 g, 0.90 mol) was added. The mixture was allowed to

warm to room temperature and stirred for an additional 24 hr.

The sodium carbonate was removed by filtration and the methylene

chloride was removed by evaporation at reduced pressure at

25° on a rotary evaporator. The residual oil was slurried

with a small amount of ethanol and filtered to yield 32.5 g

(74%) of 33 with mp 106-8° and nmr (CDCl$_3$) δ 2.65 (s, 6),

5.30 (d, 2) and 6.16 (d, 2).

Anal. Calcd for C$_9$H$_{10}$N$_2$O$_3$: C, 55.66; H, 5.19; N, 14.42.

Found: C, 55.87; H, 5.38; N, 14.41.

Dimethyl 4H,7H-dihydro-1,3-diacetylbenzimidazolone-5,6-

dicarboxylate. Dimethylacetylenedicarboxylate (38.4 g,

0.27 mol) and 33 (52.2 g, 0.269 mol) were stirred in 350 ml

of methylene chloride at room temperature for 24 hr. The

solvent was removed at reduced pressure. A small amount of

ethanol was added and the mixture was cooled to 5°. The

crystals were filtered to yield 90 g (99%) of product with mp

174-8° and nmr (CDCl$_3$) δ 2.65 (s, 6), 3.82 (s, 6), 3.38 (s, 4).

Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_7$: C, 53.57; H, 4.79; N, 8.32.

Found: C, 53.81; H, 4.97; N, 8.20.

Dimethyl 1,3-diacetylbenzimidazolone-5,6-dicarboxylate.

Dimethyl 4H,7H-dihydro-1,3-diacetylbenzimidazolone-5,6-di-

carboxylate (90 g, 0.265 mol) and DDQ (61.3 g, 0.27 mol)

were added to 1000 ml of benzene. The mixture was stirred

at room temperature for 24 hr. The mixture was filtered to

yield 58 g of reduced DDQ (DDQH$_2$). The liquid was removed
by evaporation at reduced pressure and a small amount of
ethanol was added. The crystals which formed were filtered
to yield 61 g (67%) of product with mp 202-4° and nmr (CDCl$_3$)
2.80 (s, 6), 3.93 (s, 6), 8.55 (s, 2).

Anal. Calcd for C$_{15}$H$_{14}$N$_2$O$_7$: C, 53.89; H, 4.22; N, 8.38.
Found: C, 54.08; H, 4.50; N, 8.38.

1,3-Diacetyl-4H,6H-thiopheno[d]imidazolone-5,5-dioxide
(30). Sulfur dioxide (32 g, 0.50 mol) was bubbled into
50 ml of acetone with cooling in a ice bath. Bis(4,5-exo-
methylene)imidazolone (9.7 g, 0.050 mol) was added. The
solution was stirred at ambient temperature for 48 hr.
Hydroquinone (0.1 g) was added as an antioxidant and a free
radical scavenger. The solution was cooled to 5° and the
crystals were separated by filtration. The acetone solution
was concentrated and an additional batch of crystals was
obtained. The combined crystals were recrystallized from
ethanol to yield 9.2 g (71%) of product which melted partially
at 146° with gas evolution and with total melting at 273-7°
(darkening above 200°), nmr (CDCl$_3$) δ 2.67 (s, 6), 4.40 (s,
4), and ir (KBr) 2910(w), 1755(s), 1720(vs), 1385(s), 1370(s),
1315(vs), 1230(s), 1130(s), 980(m). Upon drying the compound
lost SO$_2$ slowly and it was not possible to obtain a correct
elemental analysis.

Methyl 5-Bromovalerate. Methyl 5-bromovalerate was

prepared via the Hunsdiecker reaction of monomethyl apidic

acid using published procedures,[8] and had bp 42°/0.35 Torr.

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8) C. F. H. Allen, C. V. Wilson, Org. Syn., Coll. Vol. III,
   578

Methyl 5-iodovalerate. Methyl 5-bromovalerate (8.9 g,

0.045 mol) was added to a solution of sodium iodide (7.5 g,

0.050 mol) in 50 ml of reagent acetone. The solution was

refluxed briefly and cooled. A precipitate of sodium bromide

formed. The mixture was poured into 200 ml of water and

extracted twice with 50 ml portions of ether. The combined

ether layers were washed with sodium thiosulfate and water

and dried ($MgSO_4$). The ether was removed at reduced pressure

to yield 9.9 g of product (90%) with nmr ($CDCl_3$) δ 1.7-2.1

(m, 4), 2.35 (t, 2), 3.19 (t, 2), 3.67 (s, 3).

Attempted Alkylation of 30 with Methyl 5-Bromovalerate.

Lithium Di-iso-propylamide. Di-iso-propylamine (0.253 g,

0.353 ml, 2.50 mmol) was added to 20 ml of THF at -78°.

Butyllithium (2.2 M, 1.15 ml, 2.50 mmol) was added with

stirring to the cold solution. 30 (0.65 g, 2.5 mmol) in

25 ml of THF was added to the cold, stirred solution and the

mixture was stirred at -78° for one hr. The mixture was

allowed to warm to ambient temperature and stirred for one

hr and then methyl 5-bromovalerate (0.59 g, 3.0 mmol) was

added. The solution was stirred at room temperature for
48 hr and water (50 ml) was added. The mixture was
extracted with 50 ml of chloroform and was washed 2 times
with 100 ml portions of water. The combined aqueous fractions
were re-extracted with 2 x 100 ml portions of ethyl acetate
and the organic layers were all combined. Drying (MgSO$_4$) and
removal of the solvent at reduced pressure yielded no
recognizable products. The same results were obtained when
methyl 5-iodovalerate was used as the alkylating agent.

Attempted Alkylation of 30 with Methyl 5-Bromovalerate.
Potassium t-Butoxide. A solution of 30 (0.65 g, 2.50 mmol)
in 20 ml of dry DMSO was prepared. In another flask,
potassium t-butoxide was dissolved in an additional 20 ml
of dry DMSO with stirring. Methyl 5-bromovalerate (0.59 g,
3.00 mmol) was added to the potassium t-butoxide solution.
The solution was stirred briefly and the solution of 30 in
DMSO was added in one portion at ambient temperature. The
initially bright red solution turned yellow after about one
hr and was stirred at room temperature for a total of 24 hr.
Work-up as described for the lithium di-iso-propyl amide
alkylation attempt did not yield any of the desired product.
Methyl 5-iodovalerate also failed as the alkylating agent.

Attempted Alkylation of 30 with Methyl 5-Bromovalerate.
Potassium Hydride. A solution of 30 (1.29 g, 5.00 mmol) in
30 ml of dry DMF was prepared and the resulting solution was

was added dropwise to a stirred mixture of potassium hydride
(0.22 g, 5.0 mmol) in 10 ml of dry DMF at 0°. After the
addition was complete, the mixture was warmed to ambient
temperature and stirred for one hr. At this time methyl
5-bromovalerate (0.98 g, 5.0 mmol) in 5 ml of DMF was
added dropwise and the resulting solution was stirred at
ambient temperature for one hr. The solution was heated to
100° for one hr with stirring and was then allowed to cool.
The solution was poured into 200 ml of water and 50 ml of
saturated, aqueous NaCl was added. The reaction was worked
up as described for the alkylation attempt with lithium
di-iso-propyl amide. None of the desired product was
detected.

Ethyl 6-Bromohexanoate. 6-Bromohexanoic acid (100.3 g,
0.515 mol) and thionyl chloride 73 ml, 121 g, 1.03 mol) were
refluxed in 400 ml of benzene for 3 hr. Absolute ethanol
(143 g, 3.1 mol) was added dropwise through the condenser.
The solution was then stirred overnight and the solvent
removed at reduced pressure on a rotary evaporator. The
ethyl 6-bromohexanoate (106 g, 88%) was distilled (bp 105°/
7 Torr) and had nmr (CDCl$_3$) δ 1.27 (t, 3H, J=7 Hz), 1.62 (m,
6H), 2.32 (distorted t, 2H, J=6 Hz), 3.40 (t, 2H, J=6 Hz),
4.12 (q, 2H, J=7 Hz).

8-Ketononanoic Acid. This procedure is basically the
same as that used by Gaubert, Linstead, and Rydon.[5] Sodium

(10.8 g, 0.47 mol) was added to 100 g of absolute ethanol.
The mixture was stirred with ice-bath cooling until vigorous
gas evolution had subsided. Freshly distilled ethylaceto-
acetate (63.8 g, 0.49 mol) was added and the mixture was stirred at
room temperature for 15 min until all of the sodium had
dissolved. Ethyl 6-bromohexanoate (112.5 g, 0.50 mol) was
added and the solution was refluxed for 12 hr. Water
(200 ml) was added and the aqueous phase was extracted twice
with 150 ml portions of ether. The organic phases were
combined and washed with water and saturated aqueous NaCl.
The ether layer was dried over $MgSO_4$ and the solvent was
removed at reduced pressure on a rotary evaporator. Distil-
lation at 0.50 Torr afforded 92.5 g (68%) of ethyl α-acetyl-
suberate, bp 140-1°/0.50 Torr (lit.[5] 200°/2-3 Torr.)

The ethyl α-acetylsuberate thus obtained (92.5 g, 0.34
mol) was refluxed for 24 hr in 200 ml of 4N HCl with vigorous
stirring. The organic phase was separated and the aqueous
phase was extracted twice with 100 ml portions of ether. The
combined organic phases were washed with water, saturated
aqueous $NaHCO_3$, and saturated aqueous NaCl and dried ($MgSO_4$).
The solvent was removed at reduced pressure on a rotary
evaporator and the residual oil was distilled to yield 36.2 g
(62%) of 8-ketononanoic acid with bp 140°/0.40 Torr (lit.[5]
148°/0.8 Torr) with nmr ($CDCl_3$) δ 1.1-2.0 (broad, 8H), 2.14
(s, 3H), 2.34 (distorted t, 4H), 11.13 (broad s, 1H).

7-Oximino-8-Ketononanoic Acid. This procedure is taken

from the preparation of biacetyl monooxime by Semon and Damerell.[9]

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9) W. L. Semon, V. R. Dammerell, Org. Syn., Coll. Vol. II,
   204 (1943).

A) Ethyl nitrite. Two solutions are prepared. Solution

I consists of sodium nitrite (8.3 g, 0.12 mol), ethanol

(3.00 g, 0.065 mol, 3.8 ml) and water to make a total volume

of 15 ml. Solution II consists of ethanol (3.00 g, 0.065 mol,

3.8 ml), sulfuric acid (5.9 g, 3.2 ml) and water to make a

total volume of 15 ml. Ethyl nitrite was generated continuously

by adding solution I to solution II dropwise with stirring.

B) 7-Oximino-8-ketononanoic acid. A solution of 8-

ketononanoic acid (17.2 g, 0.100 mol) in 200 ml of THF was

prepared. Concentrated hydrochloric acid (0.5 ml) was added

to catalyze the reaction. Ethyl nitrite as the gas prepared

as described above, was introduced into the solution with

stirring at 0° via a gas dispersion tube at a rate such that

the total addition time was approximately 30 min. The solution

was allowed to warm to room temperature and stirred overnight.[10]

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10) The gas inlet must be disconnected after addition so the
    solution won't be sucked back into the ethyl nitrite
    generating flask.

Ether (200 ml) was added and the solution was washed twice with 200 ml portions of water and dried (MgSO₄). Removal of the solvent at reduced pressure on a rotary evaporator yielded an oil which was column chromatographed on activity I silica gel (eluent: 1% acetic acid/5% absolute ethanol/benzene) to yield 7-oximino-8-ketononanoic acid (15.8 g, 0.079 mol, 79%) as an oil with nmr (CDCl₃) δ 1.1-2.1 (broad, 6H), 2.38 (s, 3H), 2.2-3.0 (broad, 4H), 10.54 (broad s, 2H).

7-Amino-8-Ketononanoic Acid.   7-Oximino-8-ketononanoic acid (10.0 g, 0.050 mol) was dissolved in 200 ml of glacial acetic acid. PtO₂ (0.20 g) was added and the mixture was hydrogenated on a Parr apparatus at 45 psi of H₂ (uptake = 0.084 mol). The crude mixture was filtered and the solvent was removed at reduced pressure on a rotary evaporator. Attempts at purification were fruitless.

Attempted Preparation of 4-Methylimidazolone-5-hexanoic Acid (38). The crude oil from the preparation of 7-amino-8-ketononanoic acid (0.050 mol scale) were dissolved in 200 ml of ethylene glycol monoethyl ether. Urea (12.0 g, 0.10 mol) was added and the solution was refluxed for 24 hr. The solvent was removed by distillation at reduced pressure and the resulting oil was dissolved in ethyl acetate (200 ml) and washed twice with 200 ml portions of water. The organic layer was dried (MgSO₄) and the solvent was removed at reduced pressure on a rotary evaporator. The crude oil thus obtained showed no trace of the desired product, 38.

BIOGRAPHICAL NOTE

W. Harry Mandeville, the son of Harry and Kathryn
Mandeville, was born in Tulsa, Oklahoma on August 3, 1949.
At the age of 10, his parents moved to Arvada, Colorado and
took him with them. After graduating from Arvada West High
School he entered the Colorado School of Mines where he was
elected a member of Tau Beta Pi, the national engineering
honor fraternity. Upon graduation from Mines, he went to
M. I. T. to pursue a graduate career in chemistry while his
parents moved to Midland, Texas. At M. I. T. he became a
member of the American Chemical Society and Sigma Xi.

The author has accepted a position at Hoffmann-La Roche
and will be married to Susan Turner in the summer.