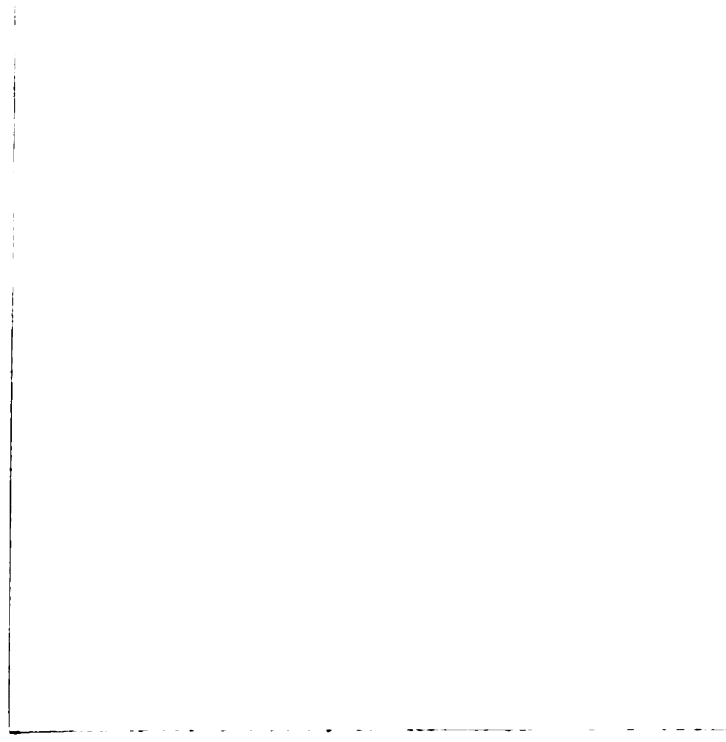
AN INVESTIGATION OF THE PRODUCT FROM CONDENSATION OF PYRUVIC ACID WITH FORMALDEHYDE

Thesis for the Degree of M. S.

MICHIGAN STATE UNIVERSITY

Ronald H. Starkey

1965

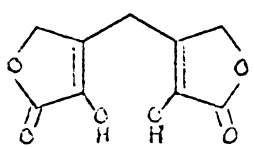


ABSTRACT

AN INVESTIGATION OF THE PRODUCT FROM CONDENSATION OF PYRUVIC ACID WITH FORMALDEHYDE

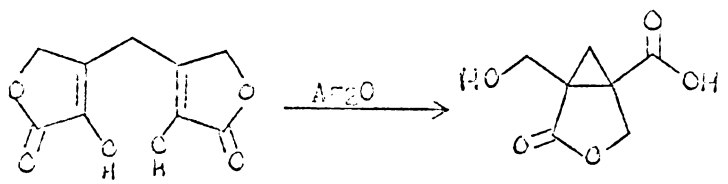
by Ronald H. Starkey

A condensation reaction of pyruvic acid with formaldehyde was first reported by O. Kaltwasser[1], who assigned an incorrect structure to the product. A reinvestigation of the reaction using modern instrumental techniques has conclusively shown the product to be I. Substantiation of I as the condensation product confirms the structure proposed by E. Asahina and S. Terada.[2]



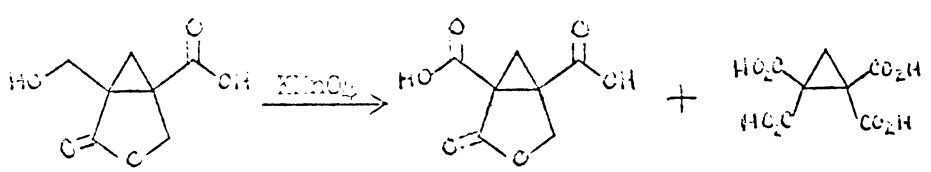
I

Also confirmed[2] was the unusual reaction in which cyclopropane ring formation occurred during a silver oxide oxidation of I, to yield II.



I II

Oxidation of II with alkaline permanganate was shown to yield III and IV, thus completing the work reported by V. Feofilaktov[3].



II III IV

REFERENCES

1. C. Maltbasser, Ber., 29, 2273 (1896).

2. E. Asahina & S.Terada, J. Pharm. Soc. (Japan), No. 502, 855 (1923).

3. V. Feofilaktov, J. Russ. Phys. Chem. Soc., 61, 1145 (1929).

AN INVESTIGATION OF THE PRODUCT FROM CONDENSATION OF PYRUVIC ACID WITH FORMALDEHYDE

By

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A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

1965

ACKNOWLEDGMENT

The author gratefully acknowledges his appreciation to Dr. William H. Reusch for his guidance and assistance during the course of this investigation.

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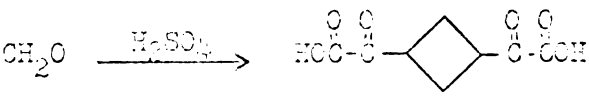
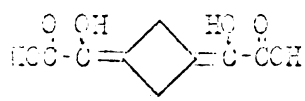
HISTORICAL AND INTRODUCTION

In 1896 C. Kaltwasser reported that pyruvic acid (I) and formaldehyde (II) yielded an acidic substance of composition $C_8H_8O_8$ when treated with concentrated sulfuric acid.[1] (Eq. 1)

(1)



I II III

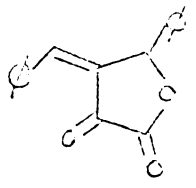


IV

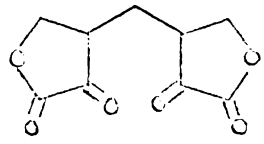
Structure III was assigned to the product on the basis of the carbon-hydrogen analysis, chemical degradation and a positive ferric chloride test, said to be indicative of enol form IV.

E. Yoshina and S. Terada repeated this work[2] in 1923 and obtained a product of exactly the same physical properties, but carbon-hydrogen analysis and neutralization equivalent determinations showed the molecular formula to be $C_4H_4O_4$. Reasoning by analogy from a reaction reported by E. Erlenmeyer[3] in which a

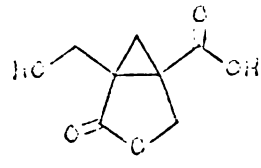
mixture of pyruvic acid and benzaldehyde saturated with hydrogen chloride yielded compound V, Asahina and Terada proposed structure VI for the condensation product.



V



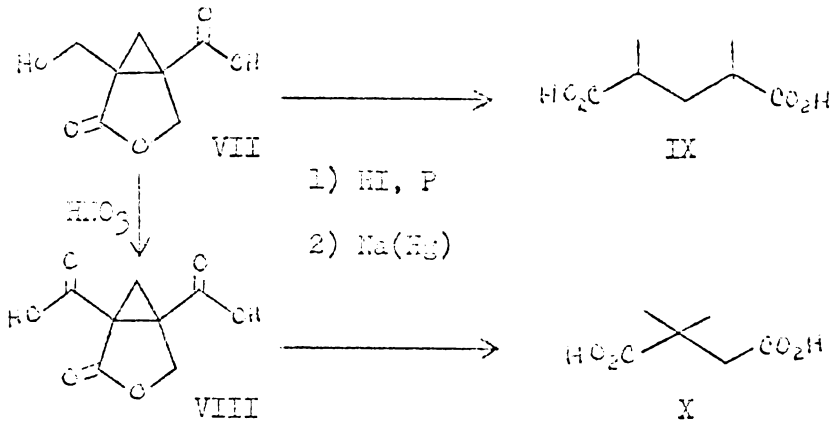
VI



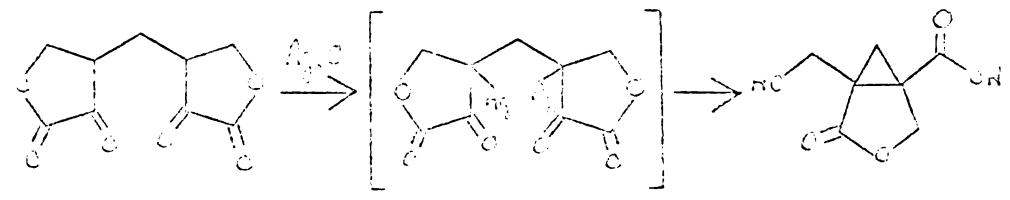
VII

Asahina and Terada also reported a remarkable reaction in which cyclopropane ring formation occurred during silver oxide oxidation of Kalthasser's acid (VI). The proposed structure of this oxidation product (VII) rested on carbon-hydrogen analysis, and conversion of VII and its nitric acid oxidation product (VIII), of melting point 219-220°, to α,α'-dimethylglutaric acid (IX) and α,α-dimethylsuccinic acid (X) respectively (Eq.2).

(2)

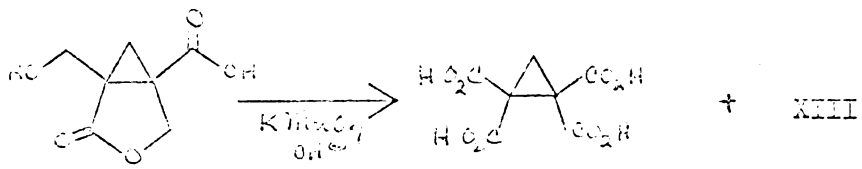


The mechanism proposed by Asahina and Terada (Eq. 3) involved the intermediate disilver complex XI, in which silver atoms are bonded to the carbons which close to form the three membered ring.

(3) 

VI XI VII

A careful investigation of the oxidation products from Kalbaumer's acid was reported in 1939 by V. Feofilaktov [4], and the formation of VII was confirmed. The most important observation in this work was that treatment of VII with alkaline permanganate (Eq. 4) gave 1,1,2,2-cyclopropanetetracarboxylic acid (VIII). This oxidation also gave another product(XIII), m.p.217, which was not identified but was assigned the molecular formula $C_6H_8O_8$ on the basis of carbon-hydrogen analysis. The structure

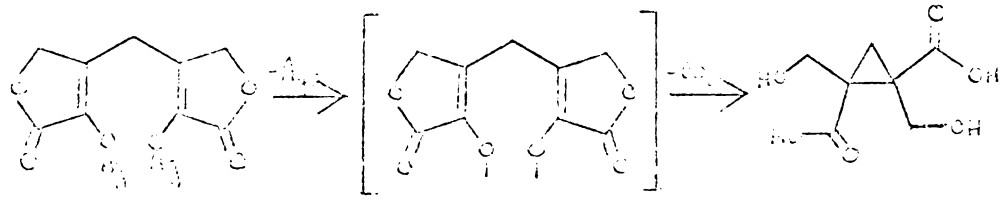
(4) 

VII VIII XIII

of XII rested on carbon-hydrogen analysis, and direct comparison with an authentic sample prepared by a malonic ester synthesis.

The mechanism proposed by Feofilaktov for the cyclopropane ring formation (Eq. 5) involved loss of CO_2 from the disilver salt of Kalbaumer's acid (XIV) to form intermediate XV, which cyclized and underwent subsequent oxidation to the substituted cyclopropane XVI.

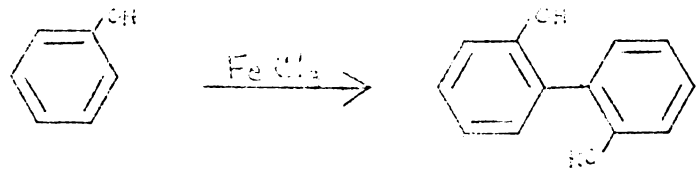
(5)



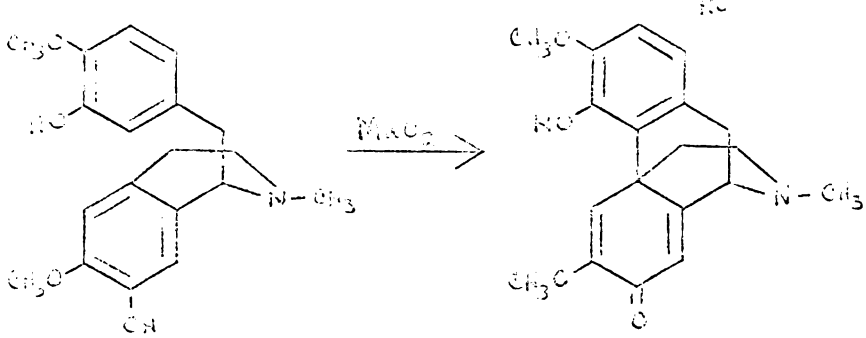
XIV XV XVI

Since there only structural assignments are known by present day standards the unusual cyclopropane ring formation described above must be viewed with skepticism. As a general rule, carbon-carbon bond formation seldom occurs during an oxidation reaction. The only well substantiated examples* of such a reaction are the oxidative coupling of phenolic compounds,[5] of which equations 6 and 7 are examples.

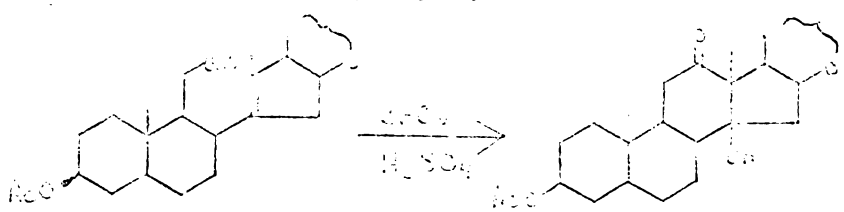
(6)



(7)



*Some cases apparently involving C-C bond formation during oxidation may actually be multistepped reactions in which the carbon bond formation occurs separately from the oxidation. An example of such a reaction is:

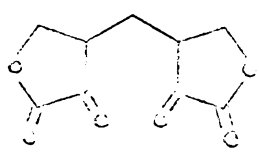


With these facts in mind, this investigation was undertaken to determine if structure VI corresponds to Kaltenbronn's acid; and if so, whether cyclopropane ring formation actually occurs in the silver oxide oxidation.

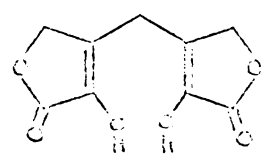
RESULTS AND DISCUSSION

A. The Condensation Reaction of Pyruvic Acid with Formaldehyde

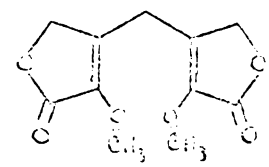
When a mixture of pyruvic acid and paraformaldehyde was treated with concentrated sulfuric acid according to the procedure of Feofilaktov,[4] a tan solid was obtained which upon crystallization from water gave white crystals, melting point 236-239°(d), (reported[4] for Kaltwasser's acid 236-238°).



VI



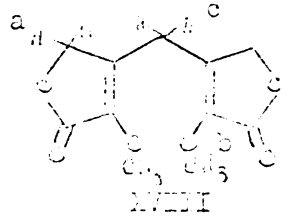
XVII



XVIII

The infrared spectrum of this material showed absorption maxima at 3310 (OH), 1725 (C=O), 1630, 1170 & 770 cm^{-1}, indicating that Kaltwasser's acid (VI) exists predominantly in the keto form XVII. Additional evidence for existing the enol form was found in the methylation of Kaltwasser's acid with diazomethane, which yielded the dimethyl ether XVIII.

Assignment of structure XVIII was based on the infrared spectrum, $\nu_{max}^{CHCl_3}$ 1780 (C=O), 1670 (C=C), 1360 (CH_3) & 1110 cm^{-1}; and the nuclear magnetic resonance (nmr) spectrum (Fig. 1). Carbon-hydrogen analysis and molecular weight determinations confirmed the molecular formula $C_{11}H_{12}O_6$.

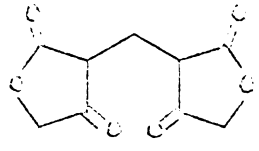


XVIII

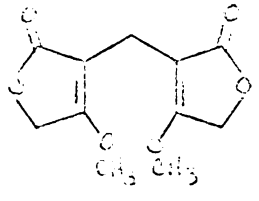
τ	area	H
5.33 (a)	2	a
7.33 (b)	3	b
8.47 (c)	1	c

Figure 1.

These for the data do not exclude the tetronic acid structure XIX, which is an isomer of Kaltwasser's acid. The tetronic acid would also react with diazomethane to yield a dimethyl ether (XX), which would have an nmr spectrum very similar to the one observed. Even more remarkable is the fact



XIX

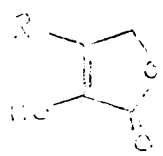


XX

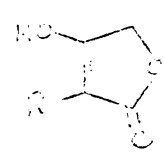
that tetronic acid XIX has been synthesized and exhibits a melting point of 235-236° [7] - the same as that of Kaltwasser's acid.

Evidence in support of structure XVIII over the tetronic acid structure may be found in the ultraviolet spectrum of Kaltwasser's acid (λ_{max}^{EtOH} 240 mμ). Conjugated dienes usually

for model structures XXI & XXII (Fig. 2), using the best available data,[8] favor structure XVII for Kulhmann's acid.



XXI



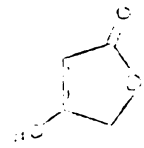
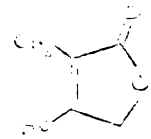
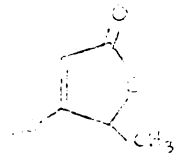
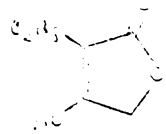
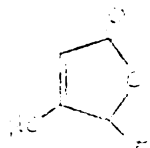
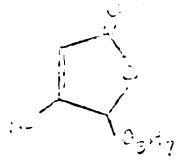
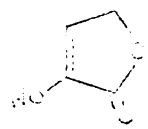
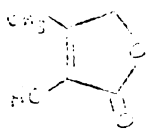
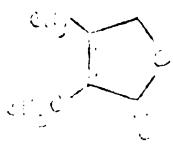
XXII

Base	215mμ	Base	215mμ
5 membered ring	-13	5 membered ring	-13
ester	-20	ester	-20
α alkyl substit.(1)	12	α alkyl substit.	12
α OH	35	β alkyl substit.	12
	214mμ	β OH	30
			245mμ

Figure 2

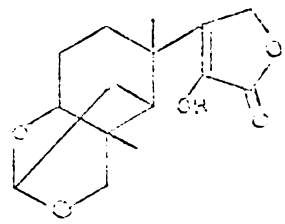
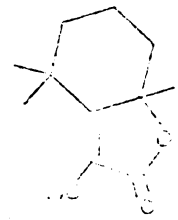
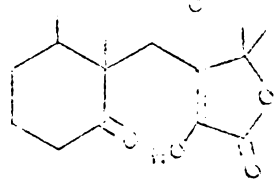
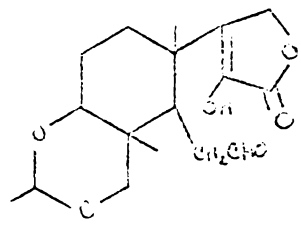
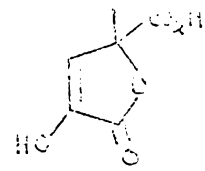
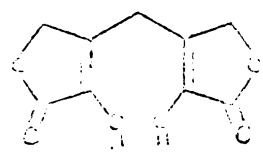
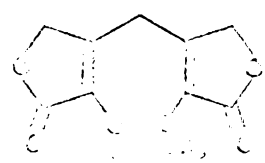
Unfortunately, the closeness of the calculated values weakens the argument, but additional evidence for deciding between the α-hydroxybutenolide (XXI) and the β-hydroxybutenolide (XXII) structures is obtained by measurement of the shift of absorption maxima observed when base is added to the sample. It is fairly well established that β-hydroxybutenolides and their derivatives exhibit a bathochromic shift of about 20 - 25mμ in base,[8,9] while the α-hydroxybutenolides show a corresponding shift of about 35 - 40mμ.[9] This shift in absorption maxima, which is illustrated by the data in table 1, is due to the formation of the enol anion in the basic media. Kulhmann's acid can thus be assigned the proposed structure (XVII) on the basis of its 46 mμ bathochromic shift in [illegible]. The method allows of both the β-hydroxybutenolide (XVII) and the α-hydroxybutenolides (XXI) differ very little in [illegible] than the parent acids.

Table 1. [illegible] of [illegible] hydroxybutenolides

	Compound	λ_{max}^{EtOH} (ε)	$\lambda_{max}^{EtOH^-}$ (ε)	$\Delta\lambda^{*}$	Ref.
1		[illegible] (12500)	[illegible] (11000)	35	9
2		250 (-)	285 (-)	35	9
3		[illegible] (12500)	[illegible] (-)	80	9
4		293 (12000)	337 (21000)	44	10
5		288 (13500)	352 (21000)	64	9
6		283 (13500)	- (-)	-	11
7		286 (4000)	321 (2000)	35	12
8		293 (12000)	- (-)	-	13
9		290 (11000)	- (-)	-	13

* Difference between λ_{max} in neutral and ethanolic KOH [illegible] added. (Difference).
** Solvent: Ethanol.

(Table I continued)

	Compound	λ_{max}^{EtOH} nm (ε)	$\lambda_{max}^{EtOH^-}$ nm (ε)	$\Delta\lambda_{max}^{+}$ nm	$\Delta\lambda_{max}^{-}$ nm
10		240 (7200)	294 (13700)	54	14
11		293 (11300)	279 (10000)	36	15
12		238 (7010)	277 (5900)	39	16
13		293 (7010)	272 (5300)	39	14
14		237 (6310)	270 (7000)	33	15
15		240 (24000)	305 (29000)	46	-
16		289 (24000)	300 (20700)	-	-

+ Bathochromic shift when 2N NaOH is added to ethanolic solution. (Table continued)

In addition to the mechanism which we have given for the formation of XIX, it may be noted that it is very difficult to construct a mechanism by which a substituted acid structure would result from the normal Mannich reaction of pyrrole with formaldehyde. On the contrary, a plausible mechanism for the condensation to yield XIX is easily written (Fig. 3).

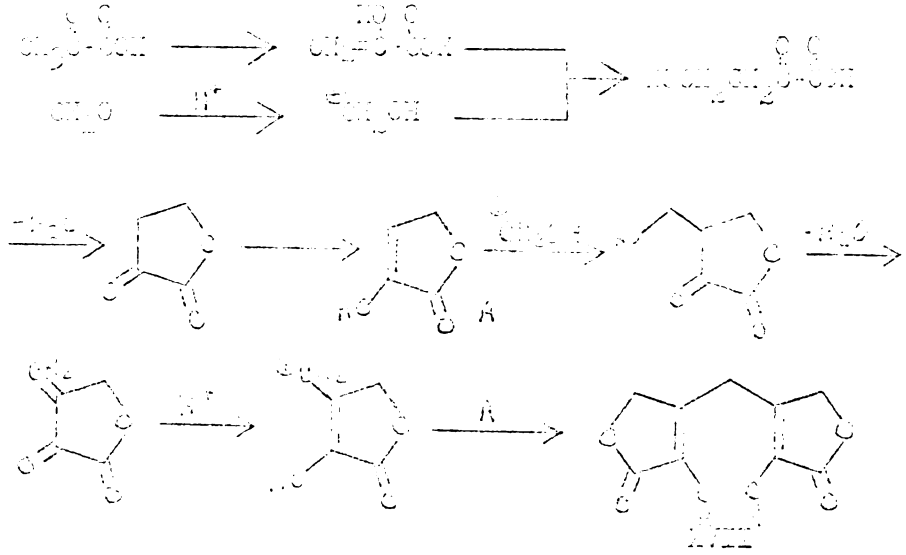
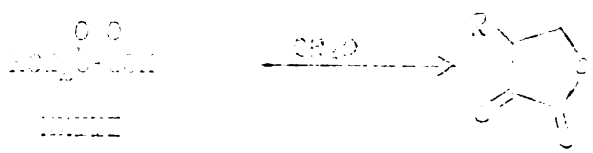
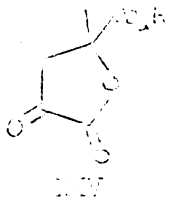


Figure 3.

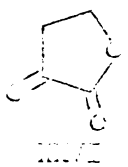
In addition to the reduction cited by Jackins & Turnbull[3] there are other analogies for the condensation. When β-substituted pyruvic acids (XXIII) were treated with formaldehyde, first in the presence of potassium carbonate followed by concentrated hydrochloric acid, products of the type XXIV were obtained.



When treated with sodium bicarbonate followed by concentrated hydrochloric acid, pyruvic acid condenses with itself to form the dilactone XIV.[27] An analogous reaction has also been observed in which pyruvic esters and diethylketone condense to yield XXVI.[28]



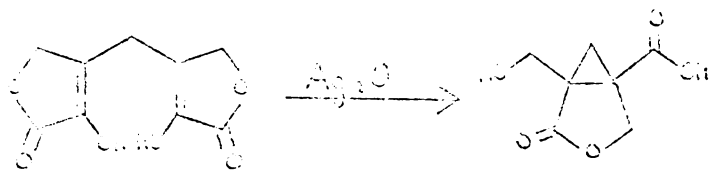
XIV



XXVI

D. The Oxidation of Kalkhasser's Acid.

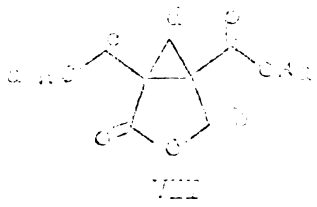
When kalkhasser's acid was oxidized by silver oxide (Eq.C) and worked up very carefully, 1-hydroxymethyl-5-carboxy-3-oxabicyclo [3.2.0] heptane-2-one (VIII), melting point 166°, was obtained.

(C) 

VIII

The analysis of material VIII by combustion was found on the Anderson system, and agrees to C7H9O5 (found for carbon) and 1745 cm^{-1} (carbonyls unit), Infrared (Fig. 1),

cyclic to the hydrogen at 9.10 and a broad peak from 9.10 - 8.80 cm^{-1}, and the nmr spectrum (Fig. 4).



VIII

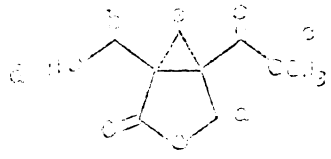
τ		Int.	Mult.	H
9.02	(d)	-	s	a
8.75	(d)	0.5	t	b
8.60	(d)	1.0	t	b
8.42	(d)	1.0	t	c
8.34	(d)	1.0	t	c
7.63	(d)	1.0	t	d
7.50	(d)	1.0	t	d

Figure 4.

Since the hydrogens on the cyclopropane ring (hydrogens d) are subject to slightly different environments, they are magnetically nonequivalent and give rise to an AB splitting pattern. In a similar manner the lactone hydrogens (hydrogens b) also exhibit an AB pattern. The methylene hydrogens of the hydroxymethyl group (hydrogens c) are adjacent to an asymmetric center and cannot become magnetically equivalent by rotation, hence an AB splitting pattern is observed here as well. Assignments of τ values to these hydrogens are based on both chemical shifts and geminal coupling constants (J_{gem}). Due to a change in the H-C-H bond angle, the J_{gem} for ring hydrogen atoms increases as the ring size increases, starting at 5 to 6 cps for cyclopropane rings and going to 12 to 13cps for six membered rings [12]. The J_{gem} in VIII are 5.[illegible] cps for the cyclopropane hydrogens, 9.5 cps for the lactone methylene, and 11.5 cps for the carbinol, ring methyl hydrogens. The magnitude of the J_{gem} [illegible] of

one Hz due to the coupling between hydrogen f and carboxylic acid proton. An additional coupling between one of the hydrogen e and hydrogen f of 1 Hz is also observed.

The ester VIII possesses three absorption bands in the carbonyl region. The three at VIII with a carbonyl group (1777), carbonyl group (1), and (1715); $\nu_{C=C}$ 1.00 (s), 3.00 (quadruplet H), 1.00 (3 double one), and 1725cm^{-1} (saturated C=O). The nmr spectrum (Figure 1) is similar to that of the acid (VIII) with additional coupling between 6.2 τ and a shift of the proton to 7.0 τ. Integration of the nmr spectrum of the acid and the corresponding methyl ester proves that VIII is a monocarboxylic acid.



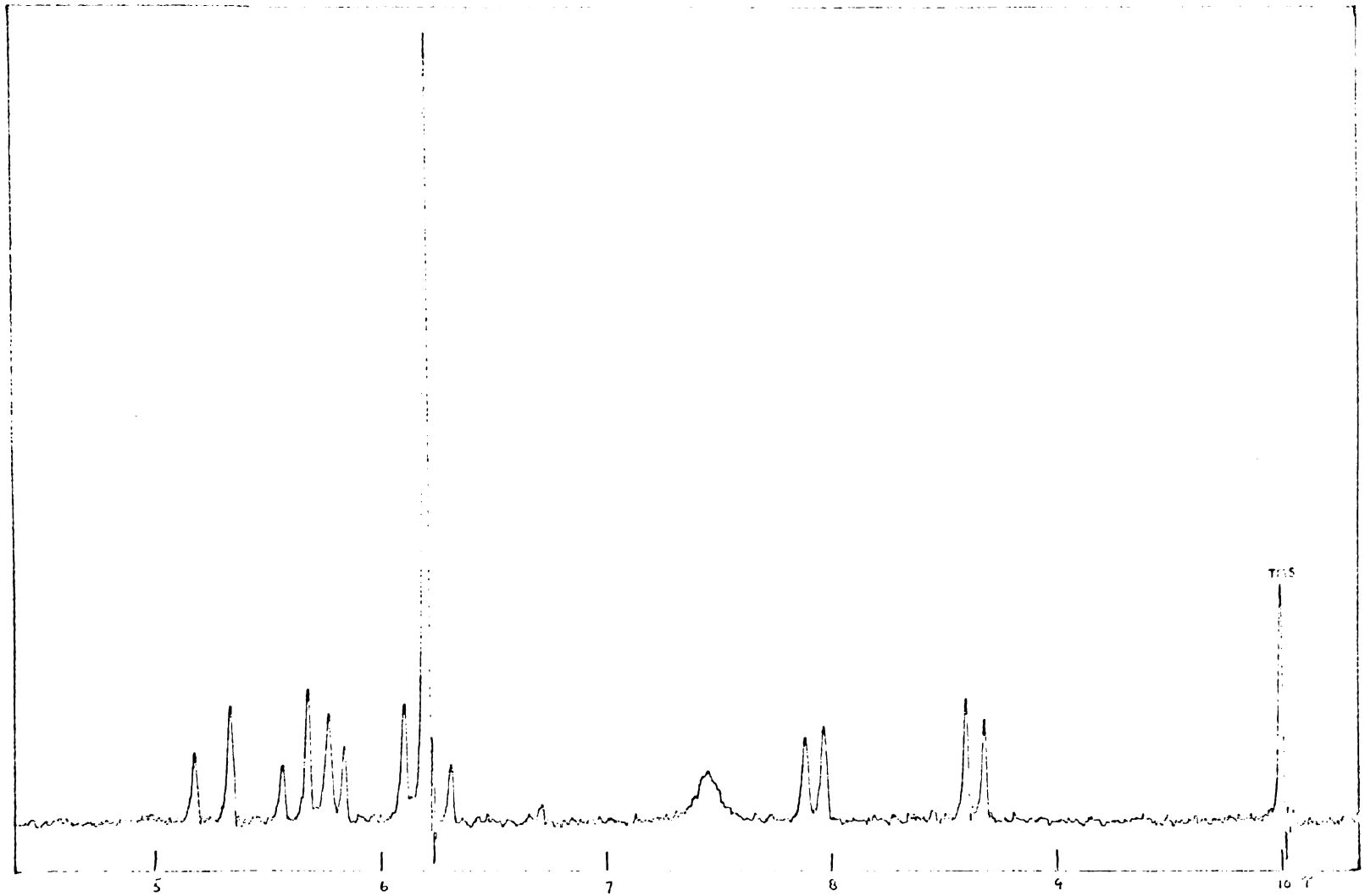
XXVII

	δ	Int	Mult	H
1	1.21 (d)	1.5	1	a
2	3.00 (d)	12.5	1	b
3	1.75 (d)	9.5	1	a
4	6.15 (s)	-	3	c
5	6.21 (d)	12.5	1	b
6	7.06 (d)	-	1	d
7	7.44 (d)	5.5	1	e
8	8.04 (d)	5.5	1	e

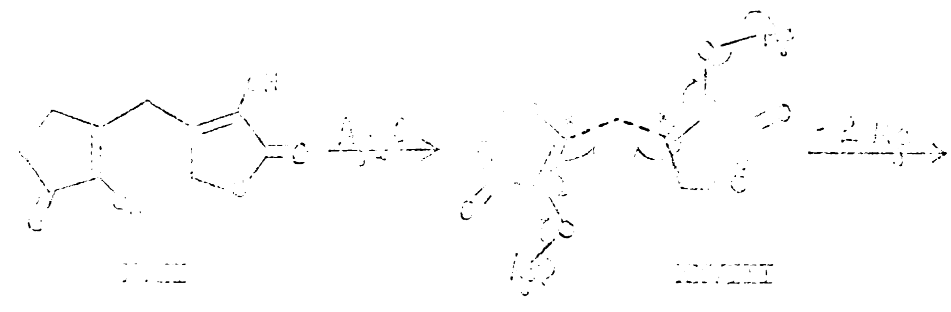
Figure 1.

the configuration of VIII as the silver oxide oxidation product since that cyclopropane ring formation does indeed take place during the silver oxide oxidation.

The [illegible] for this product VIII [illegible] (7.0 τ) indicate formation of the [illegible] acid (VIII), although [illegible] further studies

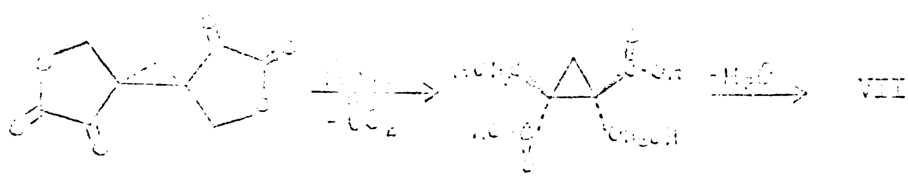

TMS
5
6
7
8
9
10
τ

concertedly or stepwise)‡ to form the three membered ring compound XXXI, followed by elimination of the [illegible] groupings by either [illegible] loss of carbon dioxide to give XXX, which [illegible] to the observed product VIII. The



XXVII XXVIII

(c)



XXIX XXX

[illegible] best suited for cyclization has the geometry shown in structure XXVIII§. In this orientation the "p" orbitals on the carbons marked by the asterisk are in very good position for overlap. The apparent absence of the stereoisomeric cyclization

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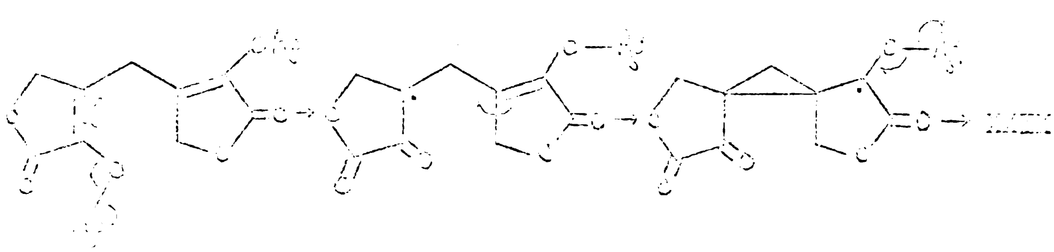
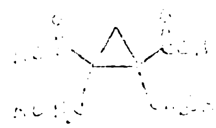
‡ The stepwise mechanism could be viewed as proceeding by:

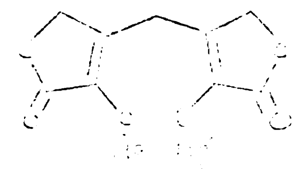


§ [illegible] the cyclopropane ring.

product having [illegible] (XXXI) is probably due [illegible], i.e. the transformation [illegible] to this [illegible] the large [illegible] atoms is on the [illegible] (XXXII).



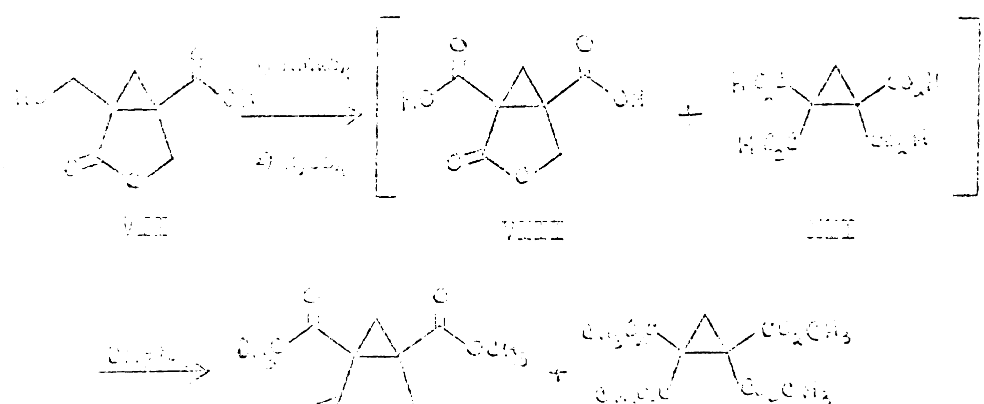
XXXI



XXXII

[illegible] VII [illegible] (eq. 10), the products [illegible] (XXXIII & XXXIV).

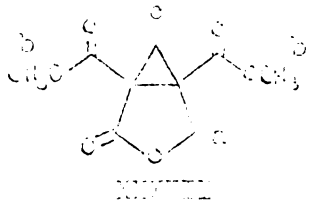
(10)



XXXIII XXXIV

The structure of XXXIII was based on the infrared spectrum, ν_{max} 3070 (cyclopropane H), 1790 (γ-lactone C=O) & 1735 cm^{-1} (ester C=O); [illegible] spectrum (Fig. 7), [illegible] the [illegible]

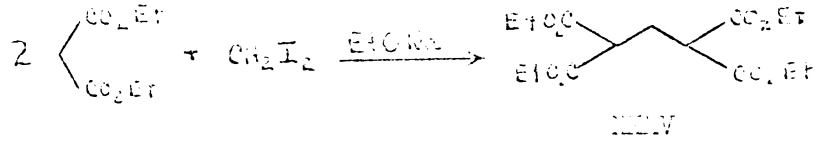
the hydrazine of the 4-nitrophenyl group. Two n.m.r. singlets from the methyl esters appeared at 6.23 and 6.27 τ.



τ		Area	Rel. no.	H
5.90	(a)	5.5	1	a
5.94	(a)	9.5	1	a
6.23	(b)	-	} 6	b
6.27	(b)	-		b
7.38	(c)	5.0	1	c
8.18	(c)	5.0	1	c

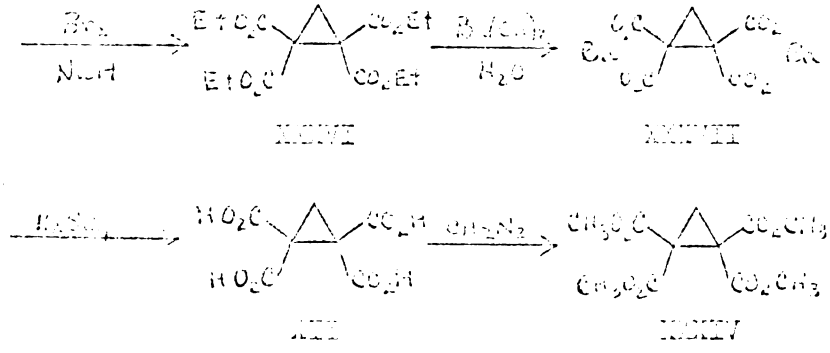
CH_2N_2 in ?.

The second product was identified as 1,1,2,2-tetracarbomethoxycyclopropane (XXXIV) by direct comparison with an authentic sample prepared by a literature ester synthesis[19] (Cf. II).



XXXIV

(11)



XXXVI XXXVII XXXIII XXXIV

All intermediate products in the synthesis of authentic XXXIV (Cf. II) were verified by infrared and n.m.r. analysis, and comparison of their physical properties with the authentic values. Authentic 1,1,2,2-tetracarbomethoxycyclopropane was characterized by the following properties: melting point [illegible]

melting point[20] 71°); infrared spectrum, ν_{max} 3100 (cyclopropyl H), 1740 (ester C=O), and 1370 cm^{-1} (methyl); and nmr spectrum, singlets at 6.23 and 7.82τ with relative areas of 6:1.

Since diazomethane is an extremely mild methylating agent for acidic hydrogens and not known to cause molecular rearrangements, the initial products of the permanganate oxidation are undoubtedly the acids VIII and XII. The identification of XXIV confirms the cyclopropane tetra-acid formation reported by Feofilaktov[4]. Comparison of the melting point of Feofilaktov's other permanganate oxidation product (XIII m.p. 217°) with that reported by Asahina and Terada for VIII(218-220°)[2], suggests that Feofilaktov's carbon hydrogen analysis was in error and that he actually obtained VIII.

EXPERIMENTAL

A. GENERAL PROCEDURES AND APPARATUS

All Infrared spectra were obtained on a Perkin - Elmer 237B Grating Infrared Spectrophotometer. Ultraviolet spectra were determined in 1cm quartz cells using a Beckman DB Spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 high resolution spectrometer, using tetramethylsilane as a reference. Vapor phase chromatography was done on an Aerograph model A-90-P Gas Chromatograph.

Melting points were determined on a Kofler hot stage melting point apparatus and are uncorrected.

Microanalysis and molecular weight determinations were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

B. Condensation of Pyruvic Acid with Formaldehyde

1. 2,6-Diketo-3,5-dihydroxymethylheptanedioic Acid Dilactone (VI & XVII), "Kaltwasser's Acid".

To a cooled (ice-salt) pasty mixture of 40.0 g. (0.455 moles) of freshly distilled pyruvic acid (b.p.$_{5mm}$ 46°) and 20.4 g. (0.680 moles) of paraformaldehyde, 48.0 ml. of concentrated sulfuric acid was added dropwise with stirring. The addition was slow enough (1 hr.) to maintain the temperature below 12°. After addition the solution was allowed to warm to room temperature, heated on a steam bath for 30 min., and allowed to stand at room temperature for 4 days. The dark brown solution (some crystals were present) was then poured into 300 ml. of water and allowed to stand for 18 hrs., during which time a tan solid precipitated. The mixture was cooled and filtered yielding about 16 g. of crude product (34%), which upon decolorization (Norit) and crystallization from water yielded 12 g. (25%) of XVII; m.p. 236-238°(d) (reported[4] m.p. 236-238°); $\bar{\nu}_{max}^{KBr}$ 3310, 1725, 1380, 1170 & 770 cm^{-1}; λ_{max}^{EtOH} 240 mμ (ε =14,200), $\lambda_{max}^{EtOH+OH^-}$ 286 mμ (ε = 17,000).

2. Methylation of 2,6-Diketo-3,5-dihydroxymethylheptanedioic Acid Dilactone.

Etheral diazomethane[21] was added slowly to a cooled ether slurry of 4.0 g. of Kaltwasser's acid (XVII) until the diazo-

methane remained in excess. After standing (2 hrs.), enough methanol was added to dissolve the crystals, and the ether and excess diazomethane were boiled away. Decolorization and crystallization from methanol yielded 2.57 g. (56%) of XVIII; m.p. 97°; ν_{max}^{KBr} 2975, 2940, 2840, 1740, 1670, 1360 & 1110 cm^{-1}; λ_{max}^{EtOH} 229 mμ (ε = 14,000), $\lambda_{max}^{EtOH+OH^-}$ 300 mμ (ε = 10,700); nmr (solvent $CDCl_3$), singlets at 5.33, 6.00 & 6.47τ, relative areas 2.0 : 2.9 : 1.0.

Anal. Calcd. for $C_{11}H_{12}O_6$: C, 54.99; H, 5.04; mole. wt., 240. Found: C, 54.91; H, 4.84; mole. wt., 257 (Rast determination).

C. Oxidation of Kaltwasser's Acid with Silver Oxide.

1. 1-Hydroxymethyl-5-carboxy-3-oxabicyclo[3.1.0]hexane-2-one (VII).

With stirring 11.4 g. of sodium hydroxide in 100 ml. of water was added to a solution of 45.0 g. of silver nitrate in 250 ml. of water and the resulting brown precipitate (Ag_2O) was washed twice (by decantation) with 300 ml. portions of boiling water, and collected by suction filtration. The damp silver oxide was then added immediately to a mixture of 6.0 g. (0.028 moles) of Kaltwasser's acid (XVII) and 120 ml. of water in a flask, equipped with true-bore stirrer and reflux condenser. The mixture was refluxed with stirring for 6 hrs., during which time a silver mirror was formed and carbon dioxide evolved.

The black insoluble material (Ag & excess Ag_2O) was removed by filtration and centrifugation, and the resulting clear yellow solution was concentrated by means of a rotoevaporator to a volume of about 50 ml. After addition of 5% HCl dropwise until it no longer precipitated any silver chloride (if an excess of HCl was added the solution could be cleared again by addition of 10% Na_2CO_3), the silver chloride was removed by centrifugation and the resulting solution was concentrated on a steam bath until crystals appeared. The light tan solid (2.0 g.), after decolorization with Norit and crystallization from acetone, yielded 1.28 g. of VI (26.4%); m.p. 186-187°; $\bar{\nu}_{max}^{KBr}$ (Fig. 8) 3440, 3100, 3000-2600 (b), 1775 & 1725 cm^{-1}; nmr (solvents D_2O and acetone d_6), broad singlet at 3.61τ relative area 2.14, closely spaced doublets at 5.35 (J=9.5cps), 5.68 (9.5), 5.75 (12.5), 6.32 (12.5), 7.95 (5.5) & 8.63τ (5.5), all with relative areas of 1.0.

2. 1-Hydroxymethyl-5-carbomethoxy-3-oxabicyclo[3.1.0]hexane-2-one (XXVII).

Etheral diazomethane was added to an ether slurry of 89.0 mg. of VII, until the solution remained yellow. After standing (1 hr.) the solution was boiled to remove excess diazomethane and concentrated until crystals began to appear. Cooling and collection yielded 80.0 mg. of white crystalline XVIII; m.p. 99-102°; $\bar{\nu}_{max}^{KBr}$ 3500, 3100, 2930, 1770 & 1725 cm^{-1}; nmr ($CDCl_3$),

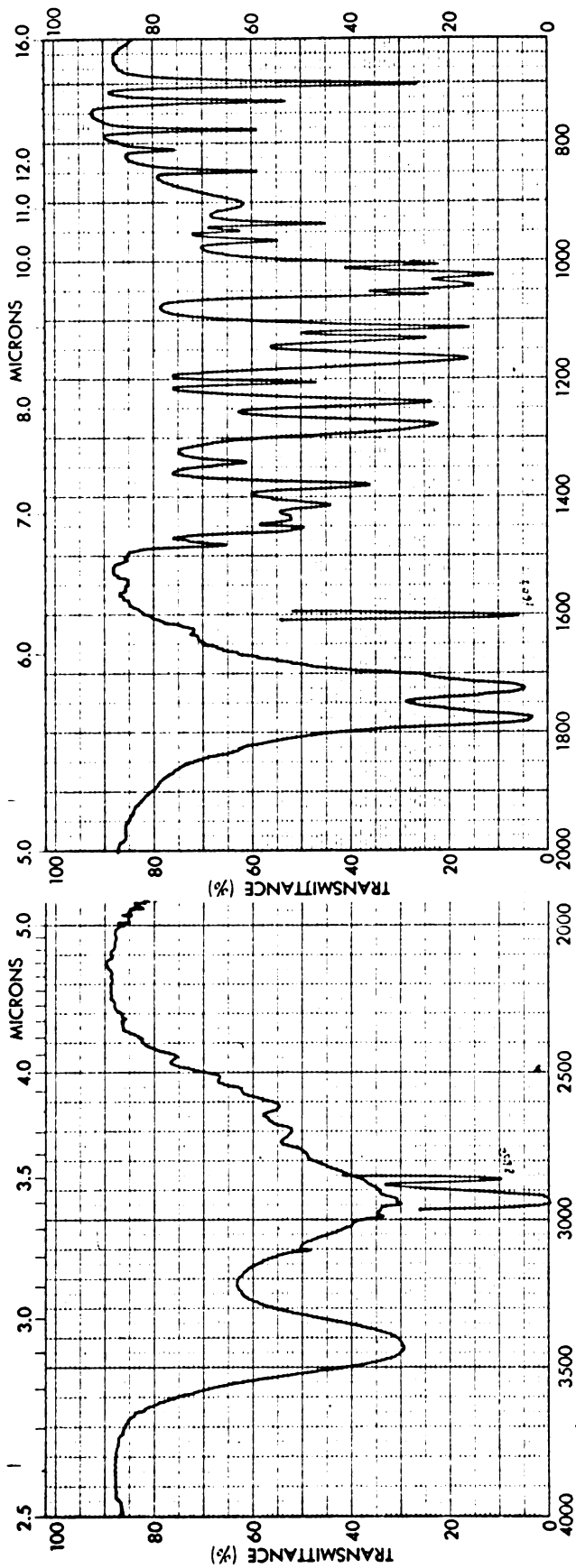


Figure 3. Infrared spectrum of 1-Hydroxymethyl-5-carboxy-3-oxabicyclo[3.1.0]hexane-2-one (VII)

singlets at 6.19 and 7.46 τ with relative areas of 3.0 : 1.0, doublets at 5.25 (J = 9.5cps), 5.68 (12.5), 5.75 (9.5), 6.21 (12.5), 7.94 (5.5) & 8.64 τ (5.5), with relative areas of 1.2 : 1.0 : 1.1 : 1.1 : 1.0 : 1.0 respectively.

D. Permanganate oxidation of 1-Hydroxymethyl-5-carboxy-3-oxabicyclo[3.1.0]hexane-2-one (VII).

A mixture consisting of 300 mg. of VII dissolved in 8.0 ml. of 5% NaOH, 300 ml. of water, and 736 mg. of potassium permanganate was refluxed until the permanganate color disappeared (5 hrs.). The MnO_2 was removed by filtration, and the resulting clear solution was concentrated (rotoevaporater) to a volume of a few milliliters, and acidified with 0.485 N H_2SO_4 (24 ml.) to a pH of about 2. The solution was then evaporated to dryness on a rotoevaporator, and the resulting solid was treated with an ether solution of diazomethane until the yellow color persisted. After standing (2 hrs.), the excess diazomethane was removed by boiling and the ether solution was washed with 5% $NaHCO_3$ and saturated NaCl solutions, and dried over $MgSO_4$. The $MgSO_4$ was removed by filtration and the solution concentrated to a volume of a few milliliters. Analysis by vapor phase chromatography on a $\frac{1}{4}$" x 5' 20% Silicone SE 20 column at 193° gave two fractions with retention times of 8 and 11 min. from ether.

1. 1,5-Dicarbomethoxy-3-oxabicyclo[3.1.0]hexane-2-one (XXXIII).

The 8 min. fraction from the vapor phase chromatography was found to be XXXIII: $\bar{\nu}_{max}^{CCl_4}$ 3090, 2950, 1790, 1735 & 1460 cm^{-1}; nmr (CCl_4), singlets at 6.23 and 6.27 τ with a combined relative area of 6.5, and doublets at 5.30 (J = 9.5cps), 5.84 (9.5), 7.52 (5.0) & 8.45 τ (5.0) with relative areas of 1.1 : 1.2 : 1.0 : 1.1 respectively.

2. 1,1,2,2-Tetracarbomethoxycyclopropane XXXIV.

Comparison of the melting point (69°) and infrared spectrum of the 11 min. fraction from vapor phase chromatography with those of an authentic sample of XXXIV showed them to be identical.

E. Synthesis of Authentic 1,1,2,2-Tetracarbomethoxycyclopropane (XXXIV).[19]

1. Methylene-bis-malonic Ester XXXV.

Freshly distilled diethylmalonate (64 g.), of boiling point 99° (@ 22 mm), was added dropwise with stirring to a dry flask containing 9.2 g. of sodium dissolved in 300 ml. of absolute ethanol (distilled from Mg).[22] To the resulting clear

solution 54.0 g. of methylene iodide (CH_2I_2) was added dropwise and the solution refluxed until no longer basic (2 hrs.). The ethanol was removed by distillation, water was added to dissolve the inorganic salts and the organic layer was taken up in ether. The ether layer was washed with water and 5% $NaHSO_3$ and dried over Na_2SO_4. After removing the ether, the remaining oil was vacuum distilled at 1.0 mm, and the resulting colorless liquid (XXXV) had the following properties: b.p.$_{1.0mm}$ 152° (reported[19] b.p.$_{12mm}$ 192°); $\bar{\nu}_{max}$ 2980, 2930, 2900, 1750 & 1730 cm^{-1}; nmr (CCl_4), quartet at 5.83τ (J 7.0 cps) with relative area of 4.0, and triplets at 6.57 (7.5), 7.64 (7.5), 8.76τ (7.0) with relative areas of 1.0 : 1.0 : 6.0.

2. <u>1,1,2,2-Tetracarboethoxycyclopropane XXXVI.</u>

A solution of 11.46 g. of XXXV in 50 ml. of benzene was added to a stirred dispersion of 3.5 g. of 52.8% sodium hydride on mineral oil, in 250 ml. of benzene (dried over NaH). Bromine was then added to the cooled solution (0°) until the bromine brown color persisted (2.1 ml. required), and the solution was refluxed for 4 hrs. After cooling, water was added slowly to destroy the excess NaH and the benzene layer was washed with water and 5% $NaHSO_3$. The liquid remaining upon removal of the benzene was vacuum distilled (b.p.$_{1mm}$ 150-166°) and found by nmr analysis to be a mixture of mono-bromo XXXV and the cyclized product XXXVI. The distillate was then added dropwise to a stirred dispersion of 1.2 g. of 52.8% NaH on

mineral oil, in 350 ml. of benzene, and refluxed for three days. After refluxing, the material was worked up as before and distilled. The 135 to 150° (@ 1.0mm) fraction was crystallized from a pentane-ether mixture and yielded 3.9 g. of XXXVI (35%). Physical properties: m.p. 43° (reported[19] 43°); $\bar{\nu}_{max}^{45°}$ 3100, 2980, 1740 & 1250 cm^{-1}; nmr (CCl_4), a quartet at 5.95τ (J 7.0cps), a singlet at 8.08τ, and a triplet at 8.85τ (J 7.0cps), with relative areas of 4.0 : 1.0 : 6.0.

3. 1,1,2,2-Cyclopropanetetracarboxylic acid XII.

A solution of 2.0 g. of XXXVI in 10 ml. of glyme and 2.29 g. of barium hydroxide in 280 ml. of water were mixed and refluxed until the mixture was no longer basic (2 hrs.). During this time the insoluble barium salt XXXVII precipitated. The solution was acidified with 0.485 N H_2SO_4 to a pH of about 2 and allowed to equilibrate. The barium sulfate was removed by filtration, the filtrate was evaporated to dryness (rotoevaporator), and the resulting white solid was taken up in hot methyl ethyl ketone. Concentration, cooling and precipitation by addition of n-hexane yielded 0.66 g. of XII (50%). Physical properties: m.p. 190-200° with decomposition and CO_2 evolution, (reported[20] m.p. 200, 208, 214, 210-212°); $\bar{\nu}_{max}^{KBr}$ 3300-2500 (b), 1725, 1420, & 1275 cm^{-1}; nmr (acetone d_6), singlets at -0.9τ and 7.87τ. Thin layer chromatography, using Silica Gel G with ethanol as the eluent, and visualizing by spraying with a saturated methanolic

solution of " Mallinkrodt IndicatAR pH 3-4 ", showed only one acid spot.

4. 1,1,2,2-Tetracarbomethoxycyclopropane XXXIV.

When 100 mg. of XII was treated with excess diazomethane, according to the procedure described previously, and crystallized from ether, 30 mg. of XXXIV (20%) was obtained. Physical properties: m.p. very sharp 69° (reported[20] 71°); $\nu_{max}^{CCl_4}$ 3100, 2950, 1740, 1435, 1370, 1240 & 1110 cm^{-1}; nmr (CCl_4), two singlets at 6.23 and 7.82τ with relative areas of 6.1 : 1.0. Vapor phase chromatography of XXXIV in an ether solution, using a 20% Silicone SE 20 column at 193°, showed only one peak (retention time 11 min. from ether). Comparison (infrared and m.p.) of the injected and collected material showed them to be identical.

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