REARRANGEMENT PRODUCTS OF
2,2',4,4',6,6'-HEXAMETHYL-4,4'-BI-4H-PYRAN

by

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INTRODUCTION

This thesis will be concerned with the acid hydrolysis products of 2,2',4,4',6,6'-hexamethyl-4,4'-bi-4H-pyran I which have been isolated up to now. It will describe the evidence for possible structures or types of structures, which is at present available for these compounds.

In considering possible structures for these products, it was assumed that the bipyran would likely hydroloyze to form a tetraketone II, as shown below. As this occurs, other steps such as aldol and Michael condensations, dehydrations, ether, acetal, and hemiacetal formations take place under the conditions of the reaction, the treatment with base, or the alumina chromatography.
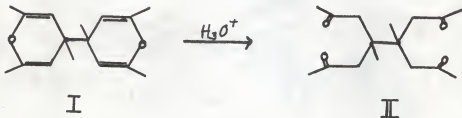
A catalogue has been prepared by K. Conrow[1a] of the various structures which could result. These were then classified by him. The essence of the approach taken in this work was to seek to eliminate most of the possible products and to choose from them one or more possible structures for each compound isolated.

Over 650 such structures appear to be possible, without considering formation of other than 5,-6, or 7 member rings, dehydration to a bridgehead atom, or changes in the skeleton.

The compounds isolated would appear to be members of a new series.

None of them have as yet been identified with any known compounds. Some of the structures suggested in the catalogue are interesting cage structures, others are basically the same as those of natural products such as tropinone, scopoline, longifolene, and santonic acid or a major part of others such as phyllocladene. Therefore, compounds such as these should prove especially interesting as possible routes to such natural products or to physiologically active compounds.

The usual approach to the problem has been to follow a mild hydrolysis by refluxing with base, then chromatography on an alumina column. After further purification of any fractions that crystallized, individual compounds were distinguished by their melting points and infra-red spectra. Then UV and n.m.r. spectra were obtained for each, and usually an analysis if there was enough pure material isolated for this.

Further information was sought from preparation of derivatives, in order to confirm the presence and determine the number of functional groups, and so that the environment of the functional groups and that of neighboring protons might be indicated by changes in their spectra. Reactions of functional groups other than the preparation of derivatives were also used for this purpose.

Since the structure of none of the compounds has been well enough established to warrant a distinctive name, each is designated by a letter of the alphabet which was assigned when the material first appeared to be a new compound.

HISTORICAL BACKGROUND

Conrow and Radlick[1] first produced 2,2',4,4',6,6'-hexamethyl-4,4'-bi-4H-pyran by a reductive dimerization of the corresponding pyrilium cation III with strong organic reducing agents. The original product was obtained from the reduction of the pyrilium perchlorate with cyclooctatetraenyl dianion. Their best results were obtained from reduction of the fluoborate salt with the potassium salt of cyclooctatetraene.

Catalytic hydrogenation of the bipyran was effected in glacial acetic acid and perchloric acid over platinum, with uptake of only 3 moles of hydrogen. The crude hydrogenation product was ketonic, but no ketone derivatives were obtained directly from the bipyran. This indicated that it was partly hydrolyzed by the acid medium and that the resulting ketone resisted further hydrogenation.

Attempts at acid hydrolysis gave intractable oils, which gave intractable mixtures of 2,4-dinitrophenylhydrazones. When the acid hydrolysis mixtures were treated with base while still fairly dilute, one could isolate various products which appeared to result from intramolecular reactions. Four such products were isolated in the pure state and characterized by means of their melting point, analysis, infrared and

ultraviolet spectra. These were designated as A, B, C, and D. Another compound E, was isolated later by K. Conrow[1a], who obtained its melting point.

Reductive dimerizations of pyrilium cations have also been obtained by Balaban and coworkers[2,3], through electrolytic methods and by the action of metals. Nearly quantitative yields of the title compound were obtained from the action of zinc dust on 2,4,6-trimethylpyrilium tetrachloroferrate. They also appeared to have obtained the 2,4,6-triphenylpyrilium dimer, m.p. 110°. No structure has yet been shown for this product.

They also did a hydrolysis of the bipyran, by refluxing in HCl, from which they obtained a product whose melting point, 139°, and infrared spectrum were different from any of those reported here. No structure was reported for this.

Several studies were made by Miss Collette Chang to see if the kinds of products and their yields would be changed when the length of the hydrolysis and the acidity of the solution were varied.

Infrared spectra and thin-layer chromatography indicated that after the first 24 hours all of the starting material had usually reacted and that the position and number of spots in the chromatograms remained about the same. As long as dilute concentrations of acid were used, the amount also did not seem to make very much difference.

Mrs. Maria Pan did several hydrolyses in which the acid hydrolysis was followed by refluxing for an hour in 10% sodium hydroxide. The hydrolyses were continued for only $1\frac{1}{2}$ to 9 hours before extracting the products and treating with base. Chromatography on activated alumina resulted in total

yields of 28% to 41% of the C, D, and E products.

Hydrolysis products of pyrilium salts themselves have been reported by Rio and Felton[7]. From a mild hydrolysis of a 2,3,5,6-tetraphenyl-pyrilium salt IV they obtained 1,2,4,5,-tetraphenyl-2-pentene-1,5-dione IVA. By heating or photolysis, they obtained a trans isomer of this product IVB. Corresponding products were obtained from other pyrilium salts, and they were able to reverse the reaction on some by the use of $FeCl_3$.
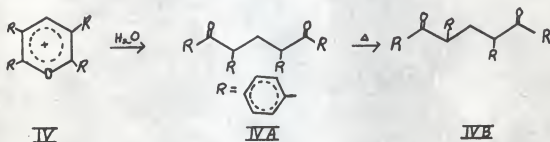
RESULTS AND DISCUSSION

General Comments

The standard procedure in the hydrolyses was, at first, to add a few drops of perchloric acid to a solution of the bipyran in a mixture of water and dioxane and allow it to stand for 24 hours. After isolation of the hydrolysis products from the reaction mixture, they were then chroma-tographed on an alumina column. The results were much the same as they were in previous attempts, when the acid solution was treated with base and refluxed before isolation of the products.

One hydrolysis was done according to the method of Balaban and

coworkers[2] by refluxing with .34 M of HCl in Ethanol for 1 hour. We did
not isolate the product reported by them but obtained 3 other products, 2
of which were the same as products E and G which had been previously
obtained. This hydrolysis method may prove more satisfactory since two
of the products were isolated without chromatography, in yields of up to
10%, and so far not as many have been mixed together. Little more was
done with it to see if larger yield or more product could be obtained from
this.

Nine products have so far been isolated from all of the various
hydrolyses, which appear to be separate compounds judging by their melting
points and spectra. Infrared spectra of the remaining oils and thin-layer
chromatography indicate still other products are produced, which have not
yet been isolated in a pure condition. Some polymeric and decomposition
products also seem to be produced. Total yields of crystalline products,
have been as high as 25 to 50%.

These compounds have as yet shown little evidence that they are
directly related to each other, in the sense that they can be intercon-
verted by gain or loss of hydroxyl, shift of a double bond, reduction, or
steric epimerization. They do still all seem to be related to the original
bipyran except that H seems to have lost a CH_4 group and the data for E
does not yet fit any structure in the catalogue. Otherwise they differ
from the original analysis only by the gain of one or two H_2O groups, if
any.

All of the n.m.r. spectra indicate two methyl groups, at near 1.0δ,
which can be assigned to the methyl groups at the 4 and 4' positions of
the original bipyran. The n.m.r. spectra also are expected to indicate the

presence of vinyl hydrogens, hydrogens α to carbonyl or other oxygen group, allylic hydrogens, hydrogens β to oxygen, and single bridgehead hydrogens.

The ultraviolet is expected, by means of Woodwards rules[13], to show the kind of conjugated system if any which is present.

The infrared spectra of the hydrolysis products give definite evidence as to the presence of hydroxyl groups, the presence of carbonyl and whether the carbonyl is likely to be conjugated, and by comparison of the complete spectrum whether the compound is different and completely separated from other products.

All of the compounds appear to have at least one carbonyl. Those which are indicated by ultraviolet to be conjugated, absorb below 1690 cm^{-1} in the infrared i.e. D,E,F,G and J. The others B,C, and H absorb at 1690 cm^{-1} or above and therefore appear to be unconjugated.

All of the infrared spectra show absorptions in the C-O stretch region from 1300 to 900 cm^{-1} which fit carbonyl, hydroxyl or ether functions, and all show absorptions between 1000 and 600 cm^{-1} which can be attributed to double bonds, although in the case of B, at least, other data indicate that there are no double bonds. The complexity of the possible structures makes it likely that not all functions will absorb exactly where expected.

Individual Hydrolysis Products

Following is a description of the data obtained for each of the compounds. Included is the structure, if any, which has been chosen from K. Conrow's catalogue[1a] as best fitting the data. Other possible

structures from this catalogue are referred to, and are shown in the appendix. Also discussed are the results of the experimental work which has been done on each compound, and how it fits or does not fit any such proposed structure. All of these structures must surely be regarded as tentative.

For each of the structures shown in the discussion, an assignment is made of the chemical shift for the hydrogens at each position, in the n.m.r. spectrum of the compound and that of its derivative. The G.v.D. Tiers table of chemical shifts[4] is used as a general guide for making these assignments.

Compound A, $C_{16}H_{24}O_3$, m.p. 69°, tail absorption only in the ultra-violet $\varepsilon^{95\% \text{ EtOH}}_{220 \text{ m}\mu}$ -670[1]. No spectra are available for the pure product, which has not been obtained pure in this work. Plate 1 shows the infrared spectrum of a product, m.p. 67-69°, which is very similar to that of an infrared spectrum of A obtained by Conrow[1a]. It is also very similar to the spectrum of C (Plate 4) except from 1400 to 900 cm^{-1}, where it shows more peaks and is not as well resolved. This difference may be due to impurity and A may prove to be impure C. A mixed melting point of the material m.p. 67-69° and C, shows little depression.

Attempts to obtain oximes or catalytic hydrogenation products, have so far yielded only oils or starting material.

Compound B, $C_{16}H_{24}O_3$, m.p. 143-144, only weak absorption in the ultraviolet, $\varepsilon^{95\% \text{ EtOH}}_{220 \text{ m}\mu}$ 530, $\lambda^{95\% \text{ EtOH}}_{max}$ 280 $(\varepsilon$ -45)[1]. The melting point compares with 119-121 previously reported[1]. The infrared spectrum of this compound is shown on Plate 2. This spectrum of a KBr mull shows a small broad peak at 3400 cm^{-1} and a maximum at 1697 cm^{-1} in the carbonyl region,

The peak at 3400 cm^{-1} disappears when a CCl_4 solution is used for the infrared indicating that it was due to water in the KBr and that B is not hydroxylic. There are peaks below 1000 cm^{-1} which might indicate unsaturation but the n.m.r. shows no vinyl hydrogens. There are also numerous peaks in the C-O stretch region between 900 and 1250 cm^{-1}. This then indicates that this is a carbonyl compound which may be unsaturated, and may have ether oxygens.

The <u>lithium aluminum hydride reduction product</u>, <u>B2LAH</u>, $C_{16}H_{26}O_3$, m.p. 85°, has been obtained. Its infrared spectrum, Plate 3, shows a strong peak at 3400 cm^{-1} and none at 1697 cm^{-1}. These changes in spectra and analysis indicate B has only one carbonyl and no hydroxyl functions. Therefore, it would seem to have two ether oxygen atoms. Comparison of the spectra for B and its reduction product also shows disappearance of peaks at 1230 and 1210 cm^{-1} and a new peak at 1050 cm^{-1}. These then can probably be assigned to ketone and the resulting secondary -OH functions. Other peaks in this region from 1200 to 1000 cm^{-1} are probably due to saturated cyclic ether functions, but one cannot make more definite assignments, since peaks are numerous in this region. One might expect that the peaks below 1000 cm^{-1} would indicate double bonds[5], however, there are more of these in the reduction product, indicating that these must also be attributed to other (C-C and C-H) vibrations. There is no absorption near 1410 or 3020 cm^{-1} and almost none at 1600-1650 cm^{-1} where one would expect conjugated H-C=C absorptions to show.

A <u>2,4-dinitrophenylhydrazine</u> <u>derivative</u>, m.p. 125-140 was obtained but attempts to purify it by recrystallization failed. Evidently the compound changes due to the acidity of the reagent, especially when

heated, and so only small amounts of impure crystalline material or amorphous material resulted.

An attempt to form the <u>oxime</u> in pyridine gave an oil whose infrared shows a broad peak at 3400 cm^{-1}, and considerable decrease in the intensity of the 1697 cm^{-1} band, to indicate that some reaction took place, but no crystalline product resulted. Strongly basic conditions gave only some starting material and more white amorphous material which did not crystallize from fresh solvent.

The compound absorbs <u>bromine</u> from CCl_4 with evolution of HBr, indicating that the absorption may be due to substitution instead of, or in addition to, absorption by double bonds. Over 3 moles of bromine were taken up in 5 minutes. Some yellow crystalline material, m.p. 110-130°, was obtained from a bromination but not enough for further characterization.

The <u>Baeyer</u> <u>Test</u> was also negative to support the evidence for a structure without any double bonds.

The results of these reactions and the evidence of the spectra would indicate that this is a monoketone with α-hydrogens active enough to be displaced by bromine, and also two ethers which hydrolyze readily in the presence of acid, as indicated by its readiness to change in the presence of the 2,4-dinitrophenylhydrazine reagent. The absence of double bonds in the structure is indicated by the negative Baeyer test, and by the absence of vinyl hydrogens in the n.m.r. spectrum.

An Iodoform test on B, gave a yellow precipitate, indicating the presence of a methyl ketone, or hydroloysis to a methyl ketone during the reaction.

N.M.R. Spectra for B and its lithium aluminum hydride reduction product, B2LAH, are shown on Plates 18 and 19 (in the appendix). Structure V (28E1 of the catalogue), shown below, seems to fit this data best. Tentative assignments for the n.m.r. positions of the hydrogens are shown with it in Table 1.

$\underline{V}$ (28E1)
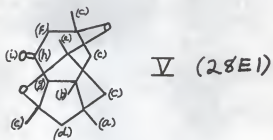
Table 1. N.M.R. Spectral assignments for hydrogens at each position.

	B				B2LAH		
Pos.	Chem. shift-δ	Theor.	Found	Pos.	Chem. shift-δ	Theor.	Found
(a&b)	0.80 and 0.92	(6)	(5.87)	(a&b)	0.89 and 0.96	(6)	(5.94)
(c)	1.32 and 1.40	(10)	(10.8)	(c)	1.22 and 1.30	(8)	
(d)	1.60 and 1.78	(2)	(1.36)	(d)	1.36 and 1.40	(4)	14.81
(e)	2.1	(3)	(3.28)	(e)	1.36 and 1.40	(3)	
(f)	2.5 and 2.7	(2)	(2.64)	(f)	1.65 and 1.78	(2)	2.47
(g)	2.9	(1)		(g)	1.92	(1)	0.66
				(h)	3.70	(1)	*
				(i)	1.55	(1)	1.15

* under dioxane sideband.

The hydrogens at position (e) in compound B would be expected to absorb below 1.5δ instead of at $2.1\ \delta^6$, which would be more normal for an α-carbonyl hydrogen. A Dreiding model of this structure is quite strained, but can be made, and there is little interaction between methyl groups or hydrogens.

The postulated reaction sequence, starting from intermediate II, would be aldol condensation between position 1 and the carbonyl at 6, and between 3 and the carbonyl at 2', then ketal formation between the resulting hydroxyls at positions 6 and 2' and the carbonyl at 6'.
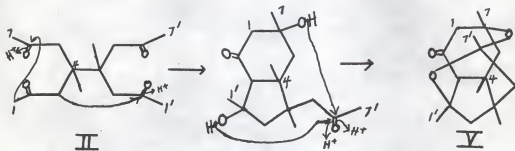
Two other possible saturated dioxa-polycycloalkanones shown in the appendix, are 387E6, and 419E6. 419E6 is a methyl ketone, but one cannot make a Dreiding model of it. All of the possible dioxa-polycycloeneones should show a vinyl hydrogen in the n.m.r. spectrum.

Compound C, $C_{16}H_{24}O_3$, m.p. 84°, has only tail absorption in the ultraviolet, $\varepsilon\ ^{95\%\ EtOH}_{220\ m\mu}\ 690^1$. The infrared spectrum (Plate 4) shows a maximum in KBr at 1690 cm^{-1}. The infrared shows no absorption at 3400 cm^{-1} with CCl_4 as solvent. From the evidence of the above spectra one would assume that this is a nonconjugated ketone with no hydroxyl function.

A 2,4-dinitrophenylhydrazine derivative, C1DNP, $C_{22}H_{28}N_4O_6$, m.p. 182-183°, indicates the presence of one carbonyl group. The infrared of this compound (Plate 5) shows absorptions at 3300, 1590, and 1615 cm^{-1} as

would be expected for the phenylhydrazine group, and there is no longer a peak at 1690 cm^{-1}, indicating complete conversion.

Attempts to produce oximes or reduction products have been unsuccessful. Apparently C is fairly stable to base, since starting material is recovered from basic reaction mixtures even after several hours, however, after longer periods only non-crystalline material was recovered from attempts to make the oxime in concentrated sodium hydroxide solutions.

When heated in pyridine with $NH_2OH \cdot HCl$, or other acidic reagents such as 2,4-dinitrophenylhydrazine reagent, only oily products were obtained from which no crystalline material was recovered. This could be due to the presence of reactive ether oxygens, which hydrolyze readily with acid present. The above information would indicate two ether and one carbonyl oxygens in the compound.

Although the infrared spectrum shows a number of peaks below 1000 cm^{-1} which might be assigned to $C=C$[5] and the n.m.r. spectrum shows a peak at 4.5 δ, the Baeyer test for double bonds proved negative. Any double bond present is apparently unreactive to the dilute potassium permanganate.

An attempt was made to determine the number of double bonds by a quantitative bromination. Almost 3 moles were absorbed from methanol in 5 minutes, however, when bromine was added in CCl_4 and allowed to stand for an hour, much more was taken up with rapid evolution of HBr. No crystalline material was recovered from these brominations.

The iodoform test for methyl ketones was negative. The infrared shows absorptions between 1350 and 1460 cm^{-1}, where methyl ketones absorb, but these could also be ascribed to other functions[5].

The n.m.r. spectrum (Plate 20) shows a peak at 4.5 δ which would

indicate either a vinyl hydrogen, or one alpha to an oxygen[6]. Two structures, VIA and VIB (167E and 7E2 of the catalogue), appear to fit the available data almost equally well, and are shown below. With them in Table 2 are shown the assignments of the hydrogens at each position and the number of hydrogens shown by the integration.
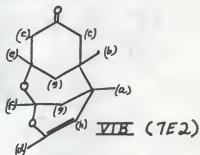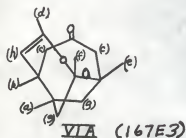
Table 2. N.M.R. Spectral assignments for hydrogens at each position.

Pos.	:	Chem. shift-δ	:	Theor.	:	Found
(a) & (b)		.80 and .87		6		5.07
(c)		1.67		4⎤		
(d)		1.67		3⎦		5.18
(e)		1.18		3		4.15
(f)		1.43		3		3.34
(g)		1.34		4		5.41
(h)		4.50		1		.81

The reaction sequence, for VIA would be: aldol between the active methyl at 1 and the carbonyl at 2', then a hemiketal between the resulting hydroxyl at 2' and the carbonyl at 6', hemiketal between the hydroxyl at 6'

and the carbonyl at 6, and finally dehydration 6 to 5.
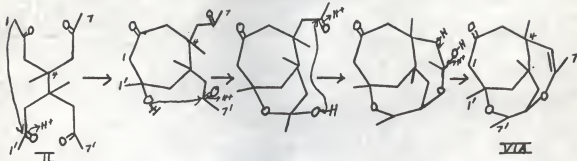
For VIB, it would be aldol-1 to 6, hemiketal-6 to 6', hemiketal-6' to 2', then dehydration 2' to 3'.
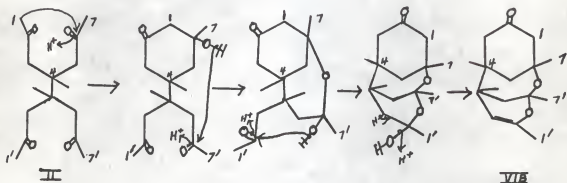
The n.m.r. assignments are generally lower than would be expected, especially for the hydrogens at position (c) which usually are above 2δ, at least in 6 or 7 member rings[6]. There does not seem to be any unusual strain. The Dreiding models are made quite easily, and show little steric interference. Other possible structures from the catalogue are 3E1, 343E6, and 343E13.

<u>Compound D</u>, $C_{16}H_{22}O_2$, m.p. 145°, $\lambda_{max}^{95\% \text{ EtOH}}$ 236 mμ (ε-9500). This ultraviolet maximum suggests a conjugated system such as that shown below, which would be calculated to absorb at 239 mμ by Woodwards rules[13].

The infrared spectrum (Plate 6, appendix) shows a very strong peak at 1637 cm^{-1}. This is also indicative of a conjugated carbonyl function, although it usually absorbs higher unless there is an ether or hydroxyl function on the system[5a]. There is no hydroxyl peak at 3400 cm^{-1} with CCl_4 as the solvent. Peaks in the C-O and C=C regions between 800 and 1200 cm^{-1} support other evidence for the presence of ether and double bond functions in the molecule.

A <u>catalytic</u> <u>hydrogenation</u> <u>product</u>, <u>D4H</u>, $C_{16}H_{26}O_2$, m.p. 135°, was obtained. Its infrared spectrum (Plate 7, appendix) shows the disappearance of the carbonyl peak and appearance of a hydroxyl peak at 3400 cm^{-1}. Peaks at 1200 cm^{-1} in the infrared of D have almost disappeared and a new peak appears near 1050 cm^{-1} in the infrared spectra of the reduction products of D. This may be due to the reduction of the carbonyl to a secondary alcohol. Another peak near 800 cm^{-1} is much reduced, perhaps due to reduction of a vinyl ether group[5].

A <u>lithium</u> <u>aluminum</u> <u>hydride</u> <u>reduction</u> <u>product</u>, <u>D4LAH</u>, $C_{16}H_{26}O_2$, m.p. 134°, was also obtained. The infrared spectrum (Plate 8, appendix) differs from that of the previous reduction product, as does also the n.m.r. spectrum (Plate 23). Mixing the two, lowers the melting point about 20°, so they seem to be different compounds. There is some absorption yet in the infrared spectrum of this product at 1640 cm^{-1}, even though the sample was quite pure. This may be due to vinyl ether[1]. It seems reasonable to assume complete reduction of the original carbonyl group to the alcohol and that the peak remaining is due to carbon-carbon unsaturation, since the remaining absorption is much less than half. The catalytic reduction also indicates that there is only one carbonyl since there was only an

uptake of 2 moles of hydrogen, while the infrared no longer shows a carbonyl peak, and the n.m.r. no longer shows vinyl hydrogen peaks.

An attempt to form the <u>oxime</u> was made with pyridine as solvent. A small amount of product was obtained, m.p. 155-190°, whose infrared showed peaks at 3300 and 1615 cm^{-1}, indicative of oxime formation, but most of the material recovered was oils or gums which did not crystallize.

A small amount of <u>2,4-dinitrophenylhydrazine derivative</u> was obtained, m.p. 235-240. It decomposed when heated to recrystallize in ethanol or other solvents. Not enough was obtained for further characterization.

A small amount of <u>benzylidene derivative</u> was obtained, m.p. 120-140°. The infrared shows the expected peaks at 810, 1610, and 3400 cm^{-1}. This result implies methylene alpha to a carbonyl or vinylogously α-methylene.

A molecular weight determination was made on D, to see if it might be a dimer. The value as determined on an osmometer was 270, compared to 246 from the molecular formula, but that of the reference compound, benzil, was also high (216 vs. lit. value 210), so it seems to be quite definitely a monomer. Since most of the other compounds are more volatile, these, too, are probably monomers.

A yellow precipitate was produced in the <u>iodoform</u> test, indicating that D is a methyl ketone, or has a vinyl ether which would give a methyl ketone upon hydrolysis.

The n.m.r. spectra for D and its reduction products are shown on Plates 21, 22, and 23 of the appendix. Plate 21 shows two vinyl hydrogen peaks at 5.4 and 5.75 δ for D, Plate 22 shows no vinyl hydrogens for D4H, the catalytic reduction product, while what appears to be a 2-proton peak still shows at 5.42 δ in the spectrum of the lithium aluminum

hydride reduction product. Since only two moles of hydrogen were added in each case, this suggests that a carbonyl and an exocyclic double bond are reduced in the catalytic reduction, and a different double bond in the lithium aluminum hydride reduction. Only an exocyclic double bond has two hydrogens in the structures which are considered likely to form. The other oxygen atom would therefore seem to be an ether oxygen. The bands at 810, 850, and 940 cm^{-1} in the infrared are not normal for a methylene double bond but when the double bonds are vinyl to ether, they often absorb there[5].

Structure VII below (438El of the catalogue) seems to agree most closely with the present data. It would be formed from intermediate II by an aldol condensation between position 3 and the carbonyl position at 2', and between position 5' and 2, followed by a hemiketal between the hydroxyl at 2' and carbonyl at 6, and dehydration 2 to 5' and 6 to 7. Possible assignments of the peaks in the n.m.r. spectra of D and its reduction products, are shown in Table 3.
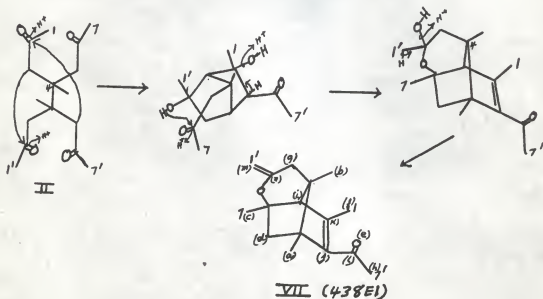

II

VII (438El)

Table 3. N.M.R. Spectral assignments for hydrogens at each position.

	D				D4H		
Pos.	Chem. shift δ	Theor.	Found	Pos.	Chem. shift δ	Theor.	Found
(a)	1.08 or 1.0	3 ⎤		(a)	1.04 or 1.20	3 ⎤	
(b)	1.08 or 1.0	3 ⎬ 8.72		(b)	1.20 or 1.04	3 ⎥ 12.70	
(c)	1.13	3 ⎦		(g)	0.98, 1.08	2 ⎥	
(d)	1.69	2 ⎤		(m)	0.92, 0.98	3 ⎦	
(i)	1.69	1 ⎦ 4.87		(h)	1.35	3	2.55
(f)	1.95	3 ⎤		(c)	1.62	3 ⎤	
(h)	1.95	3 ⎬ 6.64		(d)	1.62	2 ⎬ 5.60	
(g)	2.04,2.24,2.55	2 ⎦		(e)	1.62	1 ⎦	
(m)	5.4, 5.75	2	1.80	(f)	1.86	3	2.38
				(i)	2.02	1	0.85
				(n)	2.07	1	0.85
				(l)	4.10	1	*

D4LAH

	D4LAH						
(a)	.93 or 1.14	3 ⎤ 6.73		(j)	1.81	1	0.93
(b)	0.93 or 1.14	3 ⎦		(e)	2.10	1 ⎤	
(f)	1.32	3	3.25	(g)	2.12, 2.21	2 ⎬ 4.18	
(k)	1.52	1	1.39	(i)	2.02	1 ⎦	
(c)	1.68	3 ⎤		(l)	4.39	1	1.39
(d)	1.68	2 ⎬ 5.81		(m)	5.42	2	2.31
(h)	1.68	3 ⎦					

* not integrated

There are several inconsistencies such as the assignment at (c) which would normally be around 1.3 δ, or that at (n) which would usually be about 3.5 to 4.5 δ, and some of the integration. The molecule would be quite strained, although one can make a Dreiding model. Reduction of the double bonds may produce some longer range effects, although these are not indicated by the model. Other possible structures are 58E1, 402E1, 464E1, and 72E3, although these don't fit the changes in the n.m.r. spectrum, after reduction, and none of them are methyl ketones. The position of the hydroxyl proton in D4LAH is supported by its shift from 1.81 δ to 2.10 δ when dioxane was added.

Compound E, $C_{16}H_{22}O_2$, m.p. 99-100°, λ^{EtOH}_{max} 233 mμ ($\mathcal{E}$- 8900) and 258 mμ ($\mathcal{E}$- 4700). This ultraviolet spectrum indicates a conjugated system such as that below, which would be expected to have λ^{EtOH}_{max} at 237 and 254 mμ, according to Woodwards rules[13].
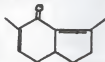
The infrared spectrum of this compound (Plate 9 of the appendix) shows a strong carbonyl peak at 1650 cm^{-1}, and only a weak peak at 3400 cm^{-1} for a KBr mull, so E is probably not hydroxylic. A double bond is indicated by several peaks between 1000 and 600 cm^{-1} and by part of the C-H band being near 3000 cm^{-1}.

A Schotten-Baumann test and an attempt to make the phenylisocyanate derivative both gave negative results, to give further evidence against the presence of hydroxyl, although since all of the hydroxyls would be tertiary, they would not form derivatives easily.

A monooxime, E1NOH, $C_{16}H_{23}O_2N$, m.p. 190°, λ^{EtOH}_{max} 245 ($\mathcal{E}$-13,000),

was obtained using pyridine as solvent. This single peak in the ultra-violet, with its greater intensity, apparently covers the same range as both maxima of E itself.

The infrared of this product (Plate 11, appendix) shows none of the original absorption at 1650 but instead shows peaks at 1620 and 3300 cm^{-1}, indicating that there is only one ketone function in compound E itself.

A reduction product, E4LAH, $C_{16}H_{26}O_2$, m.p. 151°, was obtained by lithium aluminum hydride reduction. The infrared spectrum of this compound is shown on Plate 10. This still shows peaks at 950, 875, and 805 cm^{-1} which are often associated with double bonds, either methylene or tri-substituted. The methylene double bonds usually absorb this low only when directly attached to an ether[5].

On catalytic reduction, E seems to take up about 3 moles of hydrogen to yield a small amount of impure crystals, m.p. 100-120°. Not enough pure material was obtained for more characterization except for an infra-red spectrum, which shows complete reduction of the carbonyl to the hydroxyl. The bands at 950, 875, and 805 cm^{-1}, still show.

A 2,4-dinitrophenylhydrazine derivative does form, as indicated by the infrared spectrum of the crude product, but it decomposes when heated to recrystallize and no pure product was obtained.

Compound E has been isolated both from the mild perchloric acid hydrolysis, and from a more vigorous hydrolysis in hydrochloric acid. It has been isolated both before and after chromatography on alumina, indicat-ing that it is a stable end product of the hydrolysis and is not affected by the alumina.

The n.m.r. spectra of E and its derivatives are shown on Plates 24,

25, and 26. Each of them shows a vinyl hydrogen peak of 1 or 2 protons at 5.8 to 6.9 δ. The presence of vinyl hydrogens in the lithium aluminum hydride reduction spectrum indicates that one double bond, at least, is not reduced by it.

The above evidence indicates a ketone function and at least two double bonds must be present, and in conjugation with each other. The other oxygen must be an ether oxygen. No structure could be found in the catalogue which had all of these features. Some type of skeletal rearrangement needs to be considered to account for this.

<u>Compound F</u>, no analysis, m.p. 183°, $\lambda \, ^{95\% \; EtOH}_{max}$ 242 mμ ($\mathcal{E}$-11,300). Not enough of this compound was obtained pure for analysis or derivatives. The infrared (Plate 12, appendix) shows strong peaks at 1670 and 3400 cm^{-1}. The n.m.r. (Plate 27) shows a vinyl hydrogen peak at 6.05 δ. An unsaturated hydroxy ketone is indicated, with a conjugated system such as that below, which would absorb at 239 mμ, by Woodwards rules[13]. A large number of possible structures would fit this description, for example 97 and 250 (appendix).

<u>Compound G</u>, $C_{16}H_{22}O_2$, m.p. 145°, $\lambda \, ^{95\% \; EtOH}_{max}$ 256 mμ ($\mathcal{E}$-8600) and 295 mμ ($\mathcal{E}$-5560). This would suggest a conjugated system such as that below. If it were non-coplanar, a system with the skeleton shown below would absorb at 253 and 301 mμ by Woodwards rules[13].

This partial structure does not appear in the catalogue, and the structure proposed for G (Fig. VIII), does not include the alpha substituent, but includes an extra gamma and delta substituent.

The infrared of this compound (Plate 13, appendix) shows a strong peak at 3500 cm^{-1}, and a triple peak at 1660 to 1620 cm^{-1}, which are probably due to absorbance of the carbonyl and separate absorbance of each of the conjugated double bonds. Fermi resonance seems unlikely, since there is no strong band very close to 800 cm^{-1}. This would indicate a monohydroxy dieneone. There are a number of strong peaks between 1300 and 1000 cm^{-1} which may be due to C-O stretch, and a number between 1000 and 800 cm^{-1} which can be assigned to carbon-carbon double bonds[5]. The peak at 3000 cm^{-1} also indicates unsaturated -CH.

The <u>mono-oxime</u> of this compound, $C_{16}H_{23}O_2N$, G1NOH, m.p. 174°, was obtained quite readily. The ultraviolet shows one broad absorption, $\lambda_{max}^{95\% \ EtOH}$ - 253 mμ ($\mathcal{E}$- 10500). The infrared (Plate 14) shows the expected peaks at 3500, 3300 and 1620 cm^{-1}, which would be characteristic of a hydroxy oxime, and there is no remaining peak at 1650 cm^{-1}.

<u>Attempted</u> <u>reductions</u> <u>by</u> <u>catalytic</u> <u>hydrogenation</u> <u>or</u> <u>lithium</u> <u>aluminum</u> <u>hydride</u> <u>reduction</u> yielded only small amounts of oils from which no crystalline products were isolated. An infrared of the oil from the lithium aluminum hydride reduction indicates some reduction of the carbonyl peaks at 1650 cm^{-1}. Most of the remaining spectrum was also changed.

An attempt was made to form the <u>urethane</u> <u>derivative</u> with phenyl isocyanate. A small amount of product, m.p. 110-135° was isolated, whose infrared showed a new peak at 1740 cm^{-1} and also one in the aromatic region at 760 cm^{-1}, indicating that there was some formation of the

urethane. Some starting material was also recovered.

In studying a proposed structure for this compound, structure VIII below, it was considered probable that G might undergo a dienonephenol rearrangement. For this purpose G was treated with concentrated sulfuric acid by the Kropp method[12]. Although thin-layer chromatography showed only one spot, indicating a homogeneous product, when sprayed with 2,4-dinitrophenylhydrazine reagent and ferrous chloride, only a small amount of oil and no crystalline material was obtained from the reaction. An infrared spectrum of this material no longer showed hydroxy at 3400 cm^{-1}, and still showed residual carbonyl at 1650 cm^{-1}.

The <u>iodoform test</u> was negative, which tends to support a cyclic ketone in the structure.

This product, <u>G</u>, was also isolated from the more vigorous hydrolysis brought about by refluxing 1 hour with 3 ml. of concentrated HCl in ethanol. This suggests that G may be one of the stable end products of the hydrolysis.

A possible structure for this compound is that shown in Fig. VIII below (structure 362 of the catalogue). This tricyclic conjugated diene-ol-one fits the analysis and the infrared of the compound and is consistent with the results from the chemical reactions. It does not fit the ultra-violet as well, since the mono-substituted ene-one system would be expected to absorb at 239 mu, and the diene-one system at 316[14].

N.m.r. spectra of G and its oxime (Plates 29 and 28, appendix) show vinyl hydrogen peaks at 5.81 and 6.95δ . Tentative assignments are shown below the structure. The oxime hydrogen could not be distinguished even above 8.0 δ . A shift in the position of the hydroxyl hydrogen peak, when

dioxane is added, supports the assignment for it.

The sequence of reactions which would produce this structure from intermediate II is as follows: aldol between the active methylene at 3 and the carbonyl at 2', aldol between 5 and the carbonyl at 6', then dehydration from 6 to 1 and from 6' to 5', of the resulting hydroxyls.
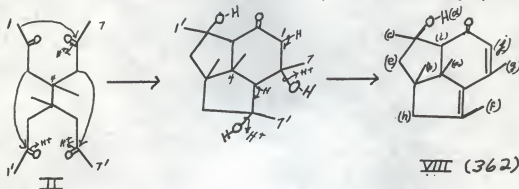

VIII (362)

Table 4. N.M.R. Spectral assignments for hydrogens at each position.

	G				G1NOH		
Pos.	Chem. shift-δ	Theor.	Found	Pos.	Chem. shift-δ	Theor.	Found
(a)	1.05 or 1.15	3	2.65	(a)	0.95 or 1.11	3	3.23
(b)	1.15 or 1.05	3	3.14	(b)	1.11 or 0.95	3	3.23
(c)	1.48	3	3.14	(c)	1.40	3	2.83
(d)	1.83	1	0.99	(d)	1.95	1	
(e)	2.09	2		(e)	2.05	2	
(f)	2.09	3	8.27	(f)	2.05	3	8.48
(g)	2.09	3		(g)	1.95	3	
(h)	2.5	2	1.65	(h)	2.45	2	2.21
(i)	2.4	1	1.15	(i)	2.28	1	1.10
(j)	5.81	1	0.99	(j)	6.95	1	*

* not integrated.

A Dreiding model of this structure shows non-coplanarity and some strain for this structure, which might explain somewhat the ultraviolet spectrum. There is, however, little steric interaction between parts of the molecule. Another possible structure is number 356 of the catalogue, shown in the appendix. Its conjugated system should absorb at 239 and 258 mμ, or even further from the value found.

<u>Compound H</u>, $C_{15}H_{22}O_4$, m.p. 186°, $\epsilon_{220 \text{ m}\mu}^{\text{EtOH}}$ - 106, tail absorption. The analysis conforms most nearly to this formula, from an average of 3 determinations. It would indicate loss of CH_4 from tetraketone structure II. A molecular weight determination on the osmometer indicated a molecular weight of 276 vs. 266 as calculated from the empirical formula. The reference compound benzil also gave a high reading of 216 vs. 210 calculated. This would indicate that H is not a dimer and that the formula is likely to be correct.

The infrared spectrum (Plate 15) shows strong peaks at 3400 and 1740 cm^{-1}, indicating an unconjugated hydroxy-ketone. Strong peaks at 940, 865, and 820 cm^{-1} would indicate the presence of double bonds[3].

When an attempt was made to do a quantitative determination of double bonds with bromine in methanol, less than a mole of bromine was taken up in 5 minutes. When bromine was added in CCl_4, there was also evolution of HBr. Some crystalline material was isolated, m.p. 125-135°, which contained halogen. The infrared of this material shows some changes in intensity of absorption, and a shoulder on the peak at 1740 cm^{-1}, but the positions of the peaks remain about the same.

A <u>lithium</u> <u>aluminum</u> <u>hydride</u> <u>reduction</u> <u>product</u>, H4LAH, $C_{15}H_{26}O_4$, m.p. 165°, was obtained. The infrared spectrum of this compound, shown on

Plate 16, shows complete disappearance of the carbonyl absorption. Absorption is greatly decreased at 1250 cm^{-1}, likely due to reduction of the carbonyl, and between 800 and 950 cm^{-1}, which would indicate reduction of a double bond.

Several attempts were made to form the oxime. Under very strongly basic conditions, a small amount of material was obtained, m.p. 255-265°, the infrared of which showed absorption at 3300 and 1600 cm^{-1}, indicating that there was some formation of oxime. Most of the product was white amorphous material, which did not crystallize after being dissolved again. A little starting material was also recovered.

The n.m.r. spectra of H and its reduction product are shown on Plates 30 and 31 of the appendix. The spectrum of H shows no peak beyond 3.22 δ, indicating that there are no vinyl hydrogens. A broad peak at 5.45 δ for the reduction product may be for a hydrogen on the same carbon as oxygen, although this is at rather low field, since normally it would be at 3.5 to 4.5 δ.

No structure is shown for this compound, as structures of this formula, involving loss of carbon, were not considered likely to form directly from the hydrolysis and were not included in the catalogue of possible structures.

Compound J, $C_{16}H_{22}O_2$, m.p. 94°, $\lambda_{max}^{95\% \text{ EtOH}}$ 253 mμ (ε-9200) and 291 (ε-8400). The ultraviolet is similar to that of G, and might indicate a similar conjugated system. This product is not as volatile as the other hydrolysis products, A to H, and sublimes readily, under vacuum, only above its melting point.

Compound J was obtained from the hydrolysis produced by refluxing in

HCl and ethanol, along with E and G. Compound J was isolated from the
pot residue, after distilling off the material which boiled between 135
and 145° at 3 mm. pressure.

The infrared spectrum (Plate 17, appendix) done on a KBr mull has 3
peaks between 1590 and 1690 indicating an unsymmetrical conjugated
diketone. A shoulder at 1410, and peaks at 860, and 940 cm^{-1} also indicate
unsaturation. There is only a small broad peak at 3300 cm^{-1} which can
usually be ascribed to water in the KBr, so there is probably no hydroxyl.

The n.m.r. spectrum (Plate 32) shows a vinyl hydrogen peak at 5.75δ.
No shift could be seen in the spectrum when dioxane was added.

From the spectral evidence one would suspect an unsymmetrical conju-
gated diketone such as in IX below (67 of the catalogue). This would be
obtained from intermediate II by an aldol between position 1 and the
carbonyl at 6, and aldol between 3 and the carbonyl at 2', then dehydra-
tion 6 to 1 and 2' to 3 of the resulting hydroxyls. Other possibilities
are structures 208, and 415 in the appendix.

II   IX (67)
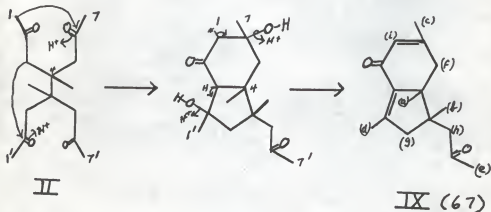
Table 5. N.M.R. Spectral assignments for hydrogens at each position.

		For J (Fig. IX)					
Pos.	Chem. shift-δ	Theor.	Found	Pos.	Chem. shift-δ	Theor.	Found
(a)	1.0 or 1.10	3	2.77	(g)	2.40, 2.58	2 ⎫	3.57
(b)	1.10 or 1.0	3	3.37	(h)	2.58	2 ⎭	
(c)	1.92	3	3.37	(i)	5.75	1	0.99
(d)	2.15	3 ⎱					
(e)	2.15	3 ⎬	7.92				
(f)	2.15, 2.22	2 ⎰					

Attempted Dimerization of
2,6,-Diphenyl-4-methylpyrilium Salts

An attempt was made to produce 2,2',6,6'-tetraphenyl-4,4'-dimethyl-4,4'-bi-4H-pyran by reductive dimerization of the corresponding pyrilium salt, with zinc. This was done to produce a simpler system which would contain fewer active hydrogens and therefore, fewer sites for condensations, when hydrolyzed. Only 20 structures could be drawn that seemed likely to form from a hydrolysis of this bipyran.

Evidently these salts hydrolyze readily in basic or neutral solutions[4] and so possibly even under the weakly acidic conditions used here. No crystalline products were isolated from these reactions.

SUMMARY

The investigations described here have shown that isolation of these

hydrolysis products is practicable and indicate that the course of the reaction is as proposed. Considerable information has been gained as to the structure of each of the compounds isolated, but further evidence is necessary to establish the structure of any of them.

Better spectra need to be obtained in some cases, as material is available, and may clear up some inconsistencies. Other evidence might be obtained by finding methods to yield derivatives where previous attempts have given little or no crystalline material. The formation of benzylidene derivatives should give more evidence as to the position of active hydrogens such as those next to carbonyl. Ozonolysis, other degradative treatment or modifications, and mass spectroscopy may be required to establish the structures.

Little work has been done on producing hydroxy derivatives of these compounds or their derivatives, in determining other reactions they will undergo, or in otherwise modifying their structure.

Further investigation is also needed to isolate and characterize all of the hydrolysis products, and to determine the most favorable conditions for producing all or any specific one of the hydrolysis products.

EXPERIMENTAL

General Points of Procedure

All melting points are uncorrected. They were taken on a Fisher-Johns melting point apparatus. All infrared spectra shown were obtained on a Perkin-Elmer 137, from KBr mulls, and the n.m.r. spectra on a

Varian A-60. The spectra included herein are shown in the appendix. The ultraviolet spectra were obtained on a Carey Model 11. The analyses were done by Galbraith Laboratories, Knoxville, Tennessee.

Unless otherwise mentioned, the 2,4-dinitrophenylhydrazine (2,4 DNP) reagent used was made up of 50 g. of 2,4-DNP in 600 ml of 85% H_3PO_4 and 395 ml. of ethanol[15].

Preparation of Starting Materials

2,4,6-Trimethylpyrilium Perchlorate was prepared essentially by the method of Diels and Alder[9]. To 308 g. of acetic anhydride, in a 1 liter erlenmeyer, at $0°$, 154 g. of 70% perchloric acid, cooled with dry ice, were added dropwise, with stirring. To this 102.5 g. of mesityl oxide were slowly added, followed by another 143 g. of acetic anhydride. The reaction mixture was then allowed to come to room temperature for an hour, then cooled again in an ice bath. After filtering and washing with acetic acid, ethanol, and ether, 69 g. of light tan crystals were obtained. The remaining solution was then heated for 15 mins. on a steam bath. After cooling and filtering, another 36 g. of darker material was obtained. The total yield was 51%. The material was not recrystallized as it was only sparingly soluble even in acetic acid.

2,2',4,4',6,6'-hexamethyl-4,4'-bi-4H-pyran (Bipyran). This was prepared in about the same way as by Balaban and coworkers[3] with modifications in the solvent. A three phase mixture of 45 g. of pyrilium perchlorate, 50 g. of zinc, 500 ml. of water, 500 ml. of petroleum ether (Skelly B, b.r. 30-60°), and 0.5 ml of 70% perchloric acid were stirred

vigorously for $3\frac{1}{2}$ hours. The petroleum ether was then separated and the aqueous layers extracted with several portions of ether. The combined ether layers were then dried over sodium carbonate and then the solvents removed. A crude yield of 23.2 g. or 93% was the best obtained. After recrystallization from ethanol, the m.p. of the product was 118°, lit. value 120-121[1]. Diethyl ether was sometimes used in the reaction instead of Skelly B, but the best yields were only about 40%, though this may have been due to other factors besides solvent.

Reactions of Bipyran

Attempted Oxime of Bipyran. To see if enol ethers would hydrolyze under conditions of oxime formation and then form oximes of the resulting carbonyls, 50 mg. of bipyran were dissolved in 0.5 ml. of pyridine together with 0.1 g. of $NH_2OH.HCl$ then refluxed for 4 hours on a steam bath. The solution had turned quite dark. After removal of the pyridine in a dessiccator over sulphuric acid, and extraction with ether, a light brown oil was obtained. No starting material or other crystalline material was separated, indicating that the material was changed, but not into a homogeneous product.

Attempted Hydrogenation of Bipyran. An attempt was made at catalytic hydrogenation in ethanol with platinum catalyst. After 24 hours at 50° and atmospheric pressure the sample was recovered unchanged.

Perchloric Acid Hydrolysis of the Bipyran. In the first hydrolyses the intention was to find the best conditions for mild acid hydrolysis and subsequent chromatography on activated alumina.

The first hydrolyses were done similarly to those of Conrow and Radlick[1] on a 1 to 4 g. scale, by adding 15 ml. of dioxane, followed by 5 ml. of water containing 10 drops of $HClO_4$ to a 1.5 g. quantity of bipyran. This was allowed to stand for 3 to 7 days, then extracted with several portions of ether. The ether portions were washed with saturated saline solution, then dried over $MgSO_4$. After standing overnight, the ether was removed and the resulting yellow oil was taken up in petroleum ether and chromatographed on activated alumina which had been further dried for a day at 100°. The treatment with sodium hydroxide was omitted.

Chromatography. The oils obtained from the hydrolysis were dissolved in Skelly B, then added to a column of approximately 30 g. of alumina per gram of sample. This was then eluted with 50 ml. portions of solvent in the order listed below. The kinds of products and the estimated total yield of each crystalline material are shown next to the fractions from which they were usually obtained.

1. Skelly B   pale oil
2. Skelly B-benzene (1:1)   - yellow oil
3. Benzene   - yellow oil   C - 160 mg.
4. Benz. - dry ether (5:1)   -   "   "
5.   "   "   (1:1)   -   "   "   B & D - 80 mg.
6. Dry ether   -   "   "
7. Dry & wet ether   (6:1)   -   "   "   E - 600 mg.
8. Dry & wet ether   (1:1)   -   "   "
9. Wet ether   - dark oil

10. Wet ether-Et. acet. (1:1) - dark oil

11. Ethyl acetate   - "   "   F & others - 180 mg.

12. Et. acet. - methanol (1:1) - "   "

13. Methanol   - "   "

The separations were incomplete in almost all fractions. Thin layer chromatography showed more than one spot for each one. Substitution of chloroform or ethanol for the ethyl acetate gave poorer results. The total yield was about 10% from 10 g. of bipyran.

Infrared spectra were found much more reliable than melting points in identification of compounds, since impure samples often melt over a narrow range considerably below the true melting point, small samples often sublime without melting, thus making identification difficult, and many of the melting points are very close together.

In one hydrolysis the material was not chromatographed and after two days some crystals formed. After separation and purification, a couple of mgs. of material were obtained, m.p. 183°. Only the infrared spectrum below 1800 cm^{-1} is available. It has the same carbonyl peak at 1690 cm^{-1} as that of F and the rest of the spectrum is also the same as that on Plate 11 of the appendix. The other material present was not identified.

The eighth hydrolysis apparently was heated too much during removal of solvent on the rotary evaporator, since it turned very dark and no crystalline material was obtained from the chromatography. Thinking this might have been due to residual acidity, the subsequent hydrolyses were dried over potassium or sodium carbonate.

Eight more hydrolyses were done on a larger scale. The hydrolyses were all continued for 24 hours before taking up the products. On one

occasion a few mgs. of starting material were recovered. The starting
material does not dissolve completely, in the amount of solvent used, until
most of it has reacted.

The last chromatography was eluted with 500 ml. portions of solvent
in the following order. Included are the initial yields of products,
before recrystallization and before rechromatography.

1.	Skelly B-benz.	(3:1)	C - 0.15 g.
2.	Skelly B-benz.-Et$_2$O	(3:1:1)	C - 2.7 g.
3.	" " "	(3:1:1)	yellow oil
4.	" " "	(2:1:2)	B & D - 0.25 g.
5.	benzene - dry ether	(2:3)	" - 0.22 g.
6.	" "	(2:3)	" - 0.12 g.
7.	" "	(2:3)	" - 0.37 g.
8.	" "	(2:3)	" - 1.08 g.
9.	" "	(1:4)	" - 0.35 g.
10.	dry ether		" - 0.25 g.
11.	"		" - 1.0 g.
12.	dry & wet ether	(19:1)	B - 0.18 g.
13.	" " "	(19:1)	B - 0.50 g.
14.	" " "	(9:1)	yellow oil
15.	" " "	(9:1)	"
16.	" " "	(5:1)	"
17.	" " "	(1:1)	"
18.	wet ether		"
19.	wet ether-ethyl Ac.	(19:1)	brown oil
20.	" "	(9:1)	"

21.	wet ether - ethyl Ac.	(4:1)	brown oil
22.	" - acetone	(9:1)	"
23.	" "	(8:1)	G - 1.0 g.
24.	" "	(4:1)	G - 0.4 g.
25.	acetone - methanol	(9:1)	dark oil
26.	" "	(1:1)	"
27.	Methanol		"

This was approximately 8.6 g. of crystalline material from 25 g. of starting material or about 34% yield. Rechromatography of some of the fractions which failed to crystallize, including those from 1 to 18 in the different hydrolyses, gave about 1 g. more of B and D, 2 g. of E, and 1 g. of H, increasing the yield to about 50%. Very little of either E or H had been obtained from any of the last hydrolyses, on the first chromatography.

Thin layer chromatography, using ether-benzene 1:1 as eluent and silica gel as stationary phase, indicates that the first 11 to 13 fractions usually contain only 1 or 2 main ketonic products. Later fractions seem to have 3 or 4 ketonic products besides tars. This is also indicated by infrared spectra and gas chromatography. Ethanol had been used in some of the earlier column chromatograms instead of acetone but it did not separate G as well and also seemed to dissolve some of the alumina.

A number of different solvent mixtures were checked on thin layer chromatography, to see which might separate B and D best. An 8:1 mixture of benzene and acetone seemed to separate these best, but it is less effective on mixtures of all of the materials.

In one chromatography where acetone was used as eluent, diacetone

alcohol was obtained from the alumina chromatography. In only one case was it observed to form in substantial amounts, but another worker in the laboratory experienced the same results.

The products were purified by recrystallization from Skelly B, benzene, cyclohexane, or ethyl acetate, and by sublimation. Compounds F, G, and H do not dissolve well in Skelly B or cyclohexane but can be recrystallized from alcohol. Ethyl acetate works well for all.

All of these products sublime readily under vacuum well below their melting points. C can be separated some from the others by this means, as it is by far the most volatile. B and D were separated some by fractional sublimation in a 16 inch glass tube under vacuum. The tube was inside another tube which was wrapped with heating wire, spaced so that the temperature of this oven gradually decreased from bottom to top. This was covered with asbestos strips and placed inside a third tube for insulation. The D was somewhat less volatile and crystallized again at a hotter temperature so that there was quite a bit of separation. More even spacing of the wiring over a longer tube would probably have given better results.

Identification and Attempted Reactions of Individual Hydrolysis Products

Compound B. This compound was identified by its infrared spectrum (Plate 2, appendix) as being the same as that previously reported[1]. However, the melting point after a number of recrystallizations was 143-144, instead of 119-121°. An ultraviolet spectrum of B showed tail absorption

to beyond 280 and the absorption maximum ($\varepsilon = 45$) at 280 mμ[1], could not be distinguished.

A 10% solution of B in CCl_4 with Me_4Si as the external standard, was used for the n.m.r. spectrum (Plate 18).

<u>Attempted oxime formation</u>. A mixture of 50 mg. of B and 50 mg. of hydroxylamine.HCl dissolved in 0.5 ml. of dry pyridine were refluxed for 2 hours on a steam bath. No crystalline material was obtained when water was added, so the solution was extracted with ether. After removal of solvents some amorphous material was obtained which softened at 50-60° but did not melt and could not be recrystallized. An infrared of this material showed a broad peak at 3400 cm^{-1}(s) and another at 1610 to 1650 cm^{-1} (m).

In another attempt a solution of 0.5 g. of NaOH in 2 ml. of water and 10 ml. ethanol was used instead of the pyridine. This was heated for 10 hours at 45°. After evaporation of the ethanol some starting material was obtained and also some colorless material which softened about 90° but did not melt and could not be recrystallized.

<u>Attempted semicarbazone</u>. A mixture of 60 mg. of B, 135 mg. of semi-carbazide.HCl, and 70 mg. of $NaHCO_3$ in 2.7 ml. of methanol and 0.1 ml. of water were refluxed for $3\frac{1}{2}$ hours on a steam bath then heated at 45° for another 21 hours. After addition of water, the original starting material precipitated.

<u>Attempted 2,4-dinitrophenylhydrazone</u> (2,4-DNP). To 80 mg. of B dissolved in 2 ml. of ethanol, were added 2 ml. of 0.2 M. 2,4-DNP reagent. After sitting overnight the crystalline material was filtered off. If the solution was neutralized with $NaHCO_3$ before filtration, some of the solid

material could be recrystallized to give crystals with m.p. 130-140°. An attempt was made to purify the remainder of the material on a silica gel column, but no crystalline material was obtained.

Lithium aluminum hydride reduction. A solution of 80 mg. of B in 20 ml. of dry ether was slowly added to 0.1 g. of lithium aluminum hydride in 20 ml. of dry ether, then refluxed for 1.5 hours at 70°. This was then hydrolyzed with 20 ml. of saturated NH_4Cl solution. The reaction mixture was then extracted with several portions of ether. After drying over Na_2CO_3 and removal of the ether, 30 mg. (37% yield) of product, m.p. 45-75° were obtained. After a number of recrystallizations from ethyl acetate and sublimation, the m.p. was 85°. The n.m.r. of this product, B2LAH (Plate 19), was obtained on a 10% solution in $CDCl_3$ with Me_4Si as an internal standard. No shift of any n.m.r. peaks could be distinguished on addition of a few drops of dioxane. The infrared (Plate 3) was also obtained. Anal. Calculated for $C_{16}H_{26}O_3$: C, 72.15%; H, 9.77%. Found: C, 71.98%; H, 9.73%.

Attempted bromination. An attempt was first made to do a double bond determination by the Kaufman iodine number method[10] by dissolving three 15 mg. samples of B in purified $CHCl_3$, then adding 5 ml. of 0.1 M. bromine in methanol and after 5 minutes 3 ml. of a 10% KI solution. The excess was then titrated with $Na_2S_2O_3$. Comparison with a blank gave an average uptake of 3.3 moles of bromine per mole of B.

When bromine in CCl_4 was added to a solution of a few mgs. of B in CCl_4, the bromine color disappeared with evolution of HBr as indicated by the white vapor formed. When bromine was added in the presence of some Na_2CO_3 to neutralize the HBr, a few yellowish crystals were obtained,

m.p. 110-130°, but not enough for further characterization.

Iodoform test. To 20 mg. of B in dioxane was added 0.2 ml. of 10%
NaOH solution and then about a ml. of KI_3 solution before the solution
remained dark. On addition of water a yellow precipitate formed. When
this was filtered off, the crystals turned brown before any were obtained
for a melting point. No starting material was isolated.

Compound C. This compound was identified with that previously
reported[1], by its melting point (83-84 vs. 82-83.5) and by its infrared
spectrum (Plate 4). The n.m.r. spectrum (Plate 20) was taken on a 10%
solution of C in CCl_4 with Me_4Si as an external standard.

Attempted oxime. A mixture of 40 mg. of C and 40 mg. of $NH_2OH.HCl$ in
1 ml. of dry pyridine was refluxed for 24 hours on a steam bath. After
addition of water and extraction with ether, some oily material was
recovered which did not crystallize. The infrared of this oil shows a
broad peak at 3300 cm^{-1} (s) and peaks at 1590 and 1630 cm^{-1} (w). Heating
for shorter periods of time (up to 4 hours) gave only some discolored
starting material, whether pyridine was used or a solution of 95% ethanol
or methanol saturated with KOH or NaOH. When impure starting material was
used, it was usually not recovered.

Attempted semicarbazone of C. A mixture of 60 mg. of C, 135 mg. of
semicarbazide.HCl, and 70 mg. of $NaHCO_3$ were dissolved in 2.7 ml. of
methanol and 1 ml. of water, then refluxed for $3\frac{1}{2}$ hours on a steam bath at
45° for 21 hours. The starting material was recovered.

Formation of a 2,4-dinitrophenylhydrazone (2,4-DNP). This was pre-
pared by adding 105 mg. of C and 80 mg. of 2,4-DNP to 12 ml. of ethanol.
This then dissolved on addition of 15 drops of concentrated H_2SO_4.

After 24 hours the resulting precipitate was filtered off. The crude yield was about 60 mg. Ethanol seemed to work best for recrystallization but only small amounts of crystals were recovered. A 3 ml. ether solution was spread on 3 thin layer silica gel plates, then developed with a 1:1 benzene-ether solution. Extraction of the main band with ether and removal of solvent gave 9 mg. of ClDNP, m.p. 190-192. Recrystallization from ethanol gave another 5 mg. of fairly pure product. An infrared was obtained (Plate 5). Anal. calculated for $C_{22}H_{28}N_4O_6$: C, 59.46%; H, 6.31%; N, 12.61%. Found: C, 59.71%; H, 6.08%; N, 12,90%.

The 2,4-DNP product decomposes quickly with acid present when heated, or even without heat if allowed to stand longer. A thin layer chromatography of the results of one attempted recrystallization showed 7 different bands of about equal intensity. Neutralization of solution with $NaHCO_3$ after completion of the reaction decreases this decomposition.

Attempted benzylidene derivative. A solution of 50 mg. of C in 0.45 ml. of a 1.7 M. NaOH in 60/40 (v/v) aqueous ethanol solution at 10°, was treated with 20 mg. of benzaldehyde. This mixture was stirred for 3 hours at between 15 and 25°. After standing 24 hours in the freezer, it was washed with $NaHSO_3$ solution. An oil separated but no crystalline material could be obtained from it other than benzoic acid.

Attempted hydrogenation. A solution of 118 mg. of C (.45 mmoles) in 6 ml. of acetic acid was added to prereduced Adam's catalyst, in a micro-hydrogenation apparatus. After 24 hours at room temperature and pressure, the apparatus indicated an uptake of 19 ml. of hydrogen (.80 mmoles). No product was recovered after removal of the acetic acid. When ethanol was used as solvent, starting material was recovered.

Attempted <u>lithium</u> <u>aluminum</u> <u>hydride</u> <u>reduction</u>. A dry ether solution of 50 mg. of C was added slowly to 50 mg. of lithium aluminum hydride in dry ether. After refluxing for 30 minutes and hydrolyzing with saturated NH_4Cl solution the starting material was recovered.

Attempted <u>bromination</u>. An attempt was made to determine the number of double bonds by using the Kaufman method[10] to determine the amount of bromine taken up from a methanol solution in 5 minutes. An average uptake of 2.64 moles of bromine per mole of C, was indicated by 3 different samples of 11 to 17 mgs. each. No crystalline material was obtained after removal of solvent.

When a solution of bromine in CCl_4 was added to 0.1 g. of C in CCl_4 over a period of 1 hour, 10 ml. of 5% solution were added before bromine color ceased to disappear. This would be an uptake of 13 moles per mole of C. There was considerable evolution of white vapors of HBr. Only oils resulted, from which no homogeneous product was recovered.

<u>Acetic</u> <u>acid</u> <u>treatment</u>. A 30 mg. sample of C in acetic acid was heated briefly, then allowed to stand for 12 hours to try to hydrolyze it. After removal of the acetic acid the sample showed only a lowering of the melting point to 60-70°. The infrared spectrum remained almost unchanged.

<u>Iodoform</u> <u>test</u>. Only a small amount of the NaOI solution was dis-colored by a sample of 20 mg. of C in dioxane. Most of the starting material was recovered.

<u>In</u> <u>the</u> <u>Baeyer</u> <u>test</u> a drop of dilute $KMnO_4$ solution was added to acetone and ethanol solutions of C. No loss of color could be observed in 5 minutes.

<u>Compound</u> <u>D</u>. This compound was identified with that previously

reported[1] by its melting point, 144-145° compared to 140-141° reported; by its infrared spectrum (Plate 6) which was the same as that previously obtained, and by the ultraviolet spectrum. The n.m.r. spectrum (Plate 21) was obtained on a 10% solution of D in CCl_4 with Me_4Si as external standard. An infrared spectrum of D in CCl_4 shows no absorption near 3400 cm^{-1}.

Attempted oxime. A mixture of 35 mg. of D, 50 mg. of $NH_2OH \cdot HCl$ and 100 mg. of KOH in 1 ml. of ethanol were refluxed for 2 hours. After removing the solvent and adding water, a gummy yellow residue was obtained which softened on heating, but did not melt. It could not be recrystallized. When heated in dry pyridine instead of alcoholic KOH, some white amorphous material was obtained. A few mgs. of powder were sublimed off which had m.p. 150-190° with decomposition. No more could be recrystallized out.

Attempted 2,4-dinitrophenylhydrazone (2,4-DNP). To a solution of 50 mg. of D in 2 ml. of ethanol were added 2 ml. of 2,4-DNP reagent. After standing for several hours, about 10 mg. of crystals were filtered off. These were recrystallized from benzene and ethanol to give a couple of mgs. of red crystals, m.p. 238-240. The infrared spectrum shows major peaks at 3350, 3000, 1650, 1500, 1430, and 1340 cm^{-1}. If the crystals were not filtered dry so that some acid was still present, they apparently hydrolyzed and only red intractable material was obtained.

Attempted benzylidene derivative. According to the method of Kohler and Chadwell[11], a solution of 25 mg. of D in 0.25 ml. of 1.7 N. NaOH in 60/40 (v/v) aqueous ethanol, was treated with 10 mg. of benzaldehyde at 10°. This was stirred at 15-30° for 3 hours. A ml. of a solution

of NaHSO$_3$ in ethanol was then added, after which the reaction mixture was allowed to stand in the freezer several days. A yellow oil separated which was chromatographed on alumina. 10 mg. of white crystals, m.p. 120-140° were obtained from the benzene fraction. The infrared shows major peaks at 3300, 2900, 1640, 1600, 1440, 1370, 1250, 1080, 960, 810, and 760 cm^{-1}. A second attempt yielded nothing but a little oil.

Hydrogenation of D. A 120 mg. sample of D in 6 ml. of acetic acid was added to prereduced Platinum catalyst in acetic acid, in a micro-hydrogenator, at room temperature and pressure. Approximately 2.6 moles of hydrogen were taken up in 13$\frac{1}{2}$ hours per mole of D. The acetic acid was then neutralized with Na$_2$CO$_3$ after which the product was extracted with ether. A 25 mg. (20%) yield of crude material was obtained, m.p. 110-130°. More material was obtained from subsequent reactions which, after several recrystallizations from Skelly B and ethyl acetate, and sublimation, had a m.p. of 134-135°. Anal. Calculated for C$_{16}$H$_{26}$O$_2$: C, 76.80%; H, 10.40%. Found: C, 76.66%; H, 10.55%.

An n.m.r. spectrum (Plate 22) was obtained on a 5% solution of D4H in CDCl$_3$ with Me$_4$Si as an external standard. When a few drops of dioxane were added, no shift could be distinguished. This spectrum was very poor. The infrared spectrum obtained is shown on Plate 7.

Lithium aluminum hydride reduction of D. A dry ether solution of 70 mg. of D was added to 100 mg. of lithium aluminum hydride in 30 ml. of dry ether. After heating at 70° for 40 minutes, the mixture was allowed to cool, then hydrolyzed with 25 ml. of saturated NH$_4$HCl solution. The yield of crude product was 25 mg. (35%). After several recrystallizations from Skelly B and ethyl acetate, pure material was obtained m.p. 133-134°.

Anal. of D4LAH: Calculated for $C_{16}H_{26}O_2$: C, 76.80%; H, 10.40%. Found: C, 76.83%; H, 10.28%.

An n.m.r. spectrum (Plate 23) was obtained on a 5% sample of D4LAH in $CDCl_3$, with Me_4Si as an internal standard. Addition of dioxane caused a shift of a 1 proton peak from 1.81 δ to 2.11 δ . The infrared spectrum obtained is shown on Plate 8.

A molecular weight determination on a Mechrolab, model 301, osmometer using chloroform as solvent and benzil as standard, gave a value of 270 for the molecular weight compared to 246 as indicated by analysis. The reading for benzil came out as 230 instead of the 222 which it should be.

Compound E. Compound E at first gave a m.p. of 94-95° similar to some material previously isolated by Dr. Conrow. Later a m.p. of 99-100° was obtained for purified material with the same infrared spectrum and same wavelength maximum in the ultraviolet. The infrared (Plate 9), ultraviolet and n.m.r. spectra all distinguished it from previous compounds. The n.m.r. spectrum (Plate 24) was obtained on a 10% solution of E in CCl_4. M.P. of the n.m.r. sample was 93-95°.

Oxime of E. A mixture of 64 mg. of E and 84 mg. of $NH_2OH \cdot HCl$ in 0.4 ml. of pyridine were heated for 3 hours on a steam bath. After cooling, water was added and 40 mg. (59%) of crude product separated. After recrystallization from benzene the m.p. was 190°. Anal. for E1NOH: Calculated for $C_{16}H_{23}NO_2$: C, 73.6%; H, 8.81%; N, 5.40%. Found: C, 73.45%; H, 8.62%; N, 5.54%.

The n.m.r. spectrum (Plate 26) was obtained from a 10% solution in $CDCl_3$ with Me_4Si as the external standard. The infrared (Plate 11) and ultraviolet spectra were also obtained.

Catalytic hydrogenation. A solution of 95 mg. of E in acetic acid was added to some prereduced platinum black in acetic acid, in a micro-hydrogenation apparatus. At room temperature and pressure there was an indicated uptake of 33.4 ml. of hydrogen in 15 hours. This was almost 4 moles per mole of E. Previous readings had not always been too reliable. The crude yield was 40 mg. (42%) of crystals, m.p. 100-120°. They were difficult to purify and not enough pure product was obtained for more than an infrared spectrum. This infrared spectrum was similar to that of the lithium aluminum hydride reduction product, shown on Plate 10. Better results were obtained from the lithium aluminum hydride reduction, so no further attempts at catalytic hydrogenation were made. An earlier attempt with ethanol as solvent gave no results.

Lithium aluminum hydride reduction. The procedure was similar to that used on B and D. After heating for $1\frac{1}{2}$ hours at 50° and hydrolysis with NH_4Cl solution, 60 mg. (67%) of product were obtained from 90 mg. of starting material. After recrystallization from ethyl acetate, the m.p. of E4LAH was 150-151°. The infrared is shown on Plate 10 and the n.m.r. spectrum on Plate 25. The n.m.r. spectrum was obtained on a 10% solution of E4LAH in $CDCl_3$ with Me_4Si as external standard. On addition of dioxane a 1 proton peak shows at 2.42 δ which could not be distinguished previously. Anal. Calculated for $C_{16}H_{26}O_2$: C, 76.80%; H, 10.40%; Found: C, 76.65%; H, 10.22%.

Attempted 2,4-dinitrophenylhydrazone (2,4-DNP). To a solution of 50 mg. of E in 2 ml. of 95% ethanol were added 2 ml. of 0.2 N. 2,4-DNP reagent. Some yellow amorphous material was obtained. When this was heated to recrystallize it, it decomposed more and no crystalline material

was obtained.

When E was allowed to stand in acetic acid for 7 hours, there was some discoloration. Thin layer chromatography did not show any new spots.

Schotten-Bauman test. About 30 mg. of E were dissolved in ethanol. Benzoyl chloride was then added, followed by enough 20% NaOH to neutralize, then shaken well. There was some oil produced but no crystalline material other than benzoic acid.

Attempted phenyl urethane. In an attempt to produce a phenyl urethane, 90 mg. of E were heated with 0.5 ml. of phenyl isocyanate for 5 mins. on a steam bath. Only diphenyl urea was recovered.

Iodoform test. A solution of 20 mg. of E in dioxane and 10% NaOH absorbed the color from about a ml. of KI_3 solution. A yellow precipitate formed on addition of water. When filtered off, the crystals were some-what reddish and on standing become more so. They melted at $100-118^\circ$ (lit. for CHI_3 119°).

Compound F. The best melting point of a sample of F, obtained by column chromatography, was $171-173^\circ$, after repeated recrystallization from benzene and ethyl acetate. The infrared spectrum (Plate 12) is very similar to that of some other material isolated without chromatography. This material had a m.p. of 183° in a sealed tube, after recrystallization and sublimation. Only the infrared spectrum below 1800 cm^{-1}, was obtained for the material isolated without chromatography. Both samples sublimed readily below their melting point at atmospheric pressure. An n.m.r. spectrum (Plate 27), was obtained on a 5% solution of the sample, m.p. $168-172^\circ$, with $CHCl_3$ as solvent. Me_4Si was used as the external standard. When the solvents were removed from the n.m.r. sample, the sample had

decomposed some. Not enough pure material was recovered for an analysis.

Compound G. After 3 recrystallizations from ethyl acetate and sublimation, the m.p. of G was 145-146°. The infrared spectrum is shown on Plate 13, the n.m.r. spectrum on Plate 29, of the appendix. The n.m.r. spectrum was obtained on a 7% solution of G in $CDCl_3$ with Me_4Si as external standard. Addition of dioxane causes a shift of a 1 proton peak from 1.83 δ. It appears then to be a shoulder on a larger peak at 2.0 . Anal. Calculated for $C_{16}H_{22}O_2$: C, 78.01%; H, 9.00%. Found: C, 78.04%; H, 8.98%.

Oxime formation. A mixture of 85 mg. of G and 150 mg. of $NH_2OH.HCl$ in 1 ml. of pyridine were heated on a steam bath for 3 hours. After cooling and adding water about 80 mg. (90%) of product were obtained. After recrystallization from ethyl acetate, the m.p. of this material, G1NOH, was 174-175°. The infrared spectrum (Plate 14) and the n.m.r. spectrum (Plate 28) were obtained. The n.m.r. sample was a 6% solution in $CDCl_3$ with Me_4Si as external indicator. No shifts could be distinguished when dioxane was added to the sample. Anal. Calculated for $C_{16}H_{23}NO_2$: C, 73.60%; H, 8.81%. Found: C, 73.38%; H, 8.59%.

Attempted hydrogenation. A solution of 50 mg. of G in 7 ml. of acetic acid was stirred vigorously with some prereduced Platinum catalyst, for 30 hours in a microhydrogenator at room temperature and pressure. There was an indicated uptake of 3.6 ml. of hydrogen, but the starting material was recovered with only slight decomposition.

Attempted lithium aluminum hydride reduction. A solution of 60 mg. of G in 30 ml. of dry ether and dimethoxyethane (glyme) was added to 0.2 g. of lithium aluminum hydride in 25 ml. of ether. This solution was

refluxed at 60° for 1½ hours. After cooling, it was hydrolyzed with NH_4Cl solution. The mixture was extracted with several portions of ether, which were dried over Na_2CO_3. Only an oil was obtained which did not crystallize. An infrared spectrum of the oil shows the same main absorptions above 1250 cm^{-1} as the starting material, though none of the spectrum is well resolved. Thin layer chromatography showed several spots for the oil.

<u>Attempted</u> <u>dehydration</u> <u>and</u> <u>phenolic</u> <u>rearrangement</u>. Following the method of Kropp[12], 30 mg. of G were heated for 30 mins. at 95° in 50% H_2SO_4 under a nitrogen atmosphere. The solution turned a dark yellow. The reaction mixture was then extracted with several portions of ether and the extracts dried over Na_2CO_3. After removal of most of the ether, the sample was chromatographed on an alumina column. The second fraction yielded a little colorless oil but no crystalline material was recovered. An infrared spectrum of the oil shows major peaks at 2900, 1660, 1450, 1375, 1260, and 890 cm^{-1} but none at 3400 cm^{-1}, and almost none between 1260 and 890 cm^{-1}.

<u>Attempted</u> <u>urethane</u>. A few mgs. of lithium were added to 10 mg. of G in dry ether, as a catalyst, as an adaptation of the method of Griffith[13]. To this was added an excess of phenyl isocyanate at room temperature. After the isocyanate had had time to react, water was added. The main product was diphenyl urea but some material was recovered by sublimation, which had a m.p. of 130-140°. This may have been mostly recovered G, but the infrared spectrum shows a broadening at 3500, a new peak at 1700 and 750 cm^{-1}, and a broad absorption from 1050-1250 cm^{-1}, as compared to the infrared of G itself.

When G was heated with phenyl isocyanate in dry pyridine for an hour, there was mainly recovery of the starting material.

In the <u>Iodoform</u> <u>test</u> on G, there was almost no absorption of Iodine and no yellow precipitate of iodoform when water was added.

<u>Compound H</u>. This material did not crystallize directly from any of the first chromatography fractions, but when Skelly B was added to the combined oils from the wet ether fractions, some of it precipitated out. When these oils were rechromatographed, more H was obtained in the same way from the acetone-methanol fractions. After washing with Skelly B and ether, recrystallization from ethyl acetate, and sublimation, the m.p. was $185-186^{\circ}$. The infrared (Plate 15) and the n.m.r. (Plate 30) were obtained. The n.m.r. was obtained on a 5% solution of H in $CDCl_3$ with Me_4Si as the internal standard. No shift of any of the n.m.r. spectrum could be observed when dioxane was added.

Anal. Calculated for $C_{16}H_{26}O_4$: C, 68.05%; H, 9.28%. for $C_{15}H_{22}O_4$: C, 67.67%; H, 8.27%. Found (avg. of 3 determinations): C, 68.03%; H, 8.01%. A molecular weight determination on the Mechrolab osmometer, using $CHCl_3$ as solvent, gave a value of 276. The calculated value for $C_{15}H_{22}O_4$ is 266. Only a dimer would come closer to fitting this formula and it does not come near the molecular weight.

<u>Lithium aluminum hydride reduction of H</u>. A dry ether solution of 70 mg. of H was added to 100 mg. of lithium aluminum hydride in dry ether. After refluxing an hour at 70° and hydrolysis, 50 mg. of crude product, m.p. $155-165^{\circ}$ were obtained. More material was prepared. After purification by chromatography and recrystallization, the m.p. was 165°. An infrared spectrum (Plate 16) and an n.m.r. spectrum (Plate 31) were

obtained. A 6% solution of H4LAH in $CDCl_3$ with Me_4Si as the internal standard was used for the n.m.r. No shift of any of the spectrum could be distinguished when dioxane was added to the sample. Anal. of H4LAH: Calculated for $C_{15}H_{26}O_4$: C, 66.67%; H, 9.63%. Found (avg. of 2 determinations): C, 66.79%; H, 9.20%.

<u>Attempted</u> <u>oxime</u>. A mixture of 60 mg. of H, 60 mg. of $NH_2OH.HCl$, and 250 mg. of KOH in 1 ml. of methanol was refluxed for 4 hours on a steam bath. After cooling, water was added. There was no precipitate, so the solution was extracted with ethyl acetate and butanol. Starting material was recovered from this, along with a few mgs. of material (m.p. 255-265° with decomposition) which had been separated by sublimation. With pyridine as solvent, only starting material was recovered. When heated for 10 hours, some white amorphous material was obtained, which did not melt below 300°.

<u>Bromination</u>. Chloroform solutions of three 15 mg. samples of H were brominated with 0.1 M bromine in methanol. The amount of bromine absorbed in 5 mins. was then determined by the Kaufman Iodine number method[10]. An average absorption of almost 1 mole of bromine per mole of H, was indicated. Separation of the chloroform layer, then removal of the solvent gave a little starting material and some other yellowish crystals, m.p. 125-135°. A Beilstein test of this material gave a green color. Major peaks in the infrared are at 3400, 2950, 1740, 1710 (sh), 1440, 1360, 1270, 1250, 1170, 1060, 995, 960, 940, 910, 875, 820, and 720. There was a change in the color of blue litmus paper when bromine in CCl_4 was added to a solution of H in CCl_4.

<u>Hydrochloric</u> <u>Acid</u> <u>Hydrolysis</u>. Following the method of Balaban and

coworkers 10 ml. of bipyran were refluxed for an hour in a solution of 3 ml. of concentrated HCl in 100 ml. of ethanol. After cooling, this was diluted with water and extracted with ether. The ether layers were washed with Na_2CO_3 solution, then dried over $MgSO_4$. After removal of the ether the resulting yellow oils were distilled at a pressure of 3 mm. Three fractions were taken off over a boiling range of $138-148°$. When no crystals appeared at first, the third fraction was chromatographed on alumina. The benzene-ether fractions of this chromatography gave some crystals which had the same m.p. and infrared as E, after purification. The tenth (methanol) fraction yielded crystals, m.p. $125-135°$, whose infrared spectrum was the same as G. Some E also crystallized out from the first two distillation fractions without chromatography.

Compound J. Crystals of J were isolated from the pot residue on addition of Skelly B, and cooling. J was recrystallized from ethyl acetate and methanol, then sublimed under vacuum at $100°$. The melting point was then $95-96°$. An infrared spectrum (Plate 17) and an n.m.r. spectrum (Plate 32) were obtained. Anal. Calculated for $C_{16}H_{22}O_2$: C, 78.01%; H, 9.00%. Found: C, 77.81%; H, 9.03%.

Gas Chromatography. Several samples were checked on the Aerograph A-90. Column chromatography fraction N20 (from wet ether-acetone) shows two main peaks at 8.7 and 26.4 mins. retention time on a $\frac{1}{4}$", diameter 6 ft. 30% cyanosilicon column at $150°$ column temperature. Fraction N25 (methanol) shows only 1 peak at 26 mins. on the same column. Gas chromatography of D4H on a $\frac{1}{4}$ in. diameter, 6 ft. silicon fluoride column; gas flow rate about 40 cc/min., at $195°$ column temperature gave 3 peaks at 36, 45, and 55 mins. retention time. This was on the sample first

recovered from the reaction mixture. The second fraction from distilla-
tion of the HCl hydrolysis products, shows two distinct peaks at 11 and
18 mins. on the silicon fluoride column at 220°.

<div align="center">Exploratory</div>

Attempted Preparation of 2,2',6,6'-Diphenyl-4,4'-methyl-bi-4H-pyran.
It was supposed that this compound could be prepared by reductive dimeri-
zation of the corresponding pyrilium salts as were the hexamethyl-bipyran
and the hexaphenyl bipyran[2].

Preparation of 2,6-Diphenyl-4-methylpyrilium Perchlorate. An attempt
was first made to produce the 2,6-diphenyl-4-methylpyrilium perchlorate
according to the method used by Praill and Whitear[7] for the formation of
other pyrilium salts. To 5.7 ml. of t-butyl-alcohol cooled to 10°, were
added 35 ml. of benzoyl chloride, with stirring. After cooling to 0° in
an ice salt bath, 1.5 ml. of 70% perchloric acid were slowly added. The
mixture was then stirred for 2 hours. No precipitate appeared, so 30 ml.
of ether were added and it was allowed to stand in the freezer overnight.
The solution was then heated on a steam bath for 15 minutes and cooled
again. No crystalline material appeared except benzoic acid.

The preparation of this pyrilium perchlorate then followed the method
of Balaban and Nenitzescu[5] in which 13 g. of aluminum chloride were slowly
added with stirring and with exclusion of moisture, to 28 g. of benzoyl
chloride in an ice bath, followed by 10.8 ml. of t-butyl-chloride.
Stirring was then continued for 5 hours. After standing overnight and
the evolution of HCl had pretty well ceased, the mixture was hydrolyzed

with a mixture of 100 g. of ice and 3.5 ml. of concentrated hydrochloric acid. After washing with ether to remove byproducts, 20 ml. of perchloric acid were added to the aqueous layer to precipitate out the yellow pyrilium perchlorate. A yield of 1.6 g. (5%) was obtained after filtration. Some of the sample was recrystallized from acetic acid in which it was slightly soluble. The m.p. of 270-272° with decomposition, agrees pretty well with the reported melting point of 270. The infrared spectrum also checked with values given. A second attempt on 4 times this scale gave a yield of 2%.

<u>Attempted</u> <u>Reduction</u> <u>of</u> <u>2,6-Diphenyl-4-methylpyrilium</u> <u>Perchlorate</u>. Several attempts were made to reduce the 6,6'-biphenyl-4-methyl pyrilium salt to the 4,4' dimer. In the first attempt, 0.2 g. of the perchlorate were added to 35 ml. of water and 0.2 g. of zinc dust, followed by 40 ml. of Skelly B and 4 drops of perchloric acid. The mixture was then stirred vigorously for 5 hours. The Skelly B layer was then separated and the water layer extracted with ether. The combined Skelly B and ether extracts were then dried over Na_2CO_3 after which the solvents were removed on a rotary evaporator. Only a red gummy substance resulted. Some of the starting material still remained in the water layer.

Other attempts involved varying the solvent or liquid phase. Acetonitrile dissolved the perchlorate better. Ethanol and mixtures of water and acetonitrile or of water and ether were also tried. Increasing the acidity, using a nitrogen atmosphere, and using $MgSO_4$ as drying agent for the ether extracts delayed formation of the red material but no other product was isolated from any of the attempts. Starting material was sometimes recovered.

The tetrachloroferrate salt was prepared by dissolving the perchlorate in concentrated HCl and adding a solution of $FeCl_3$ in concentrated HCl. This too formed only the red material. Some of the red material and some ether extracts were chromatographed on an alumina column and on silica gel thin layer. Only red gums were obtained from the column while thin layer chromatography showed only a red spot separating and a blue spot at the origin. Spraying with 2,4-dinitrophenylhydrazone and sulfuric acid showed no other spots. The red material did appear to react with the 2,4-dinitrophenylhydrazine.

ACKNOWLEDGMENT

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APPENDIX
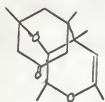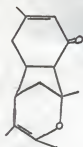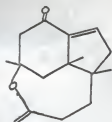
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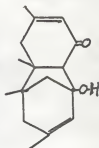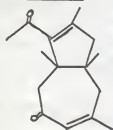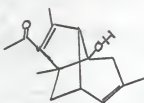
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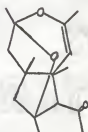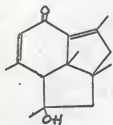
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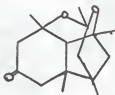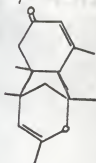
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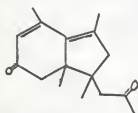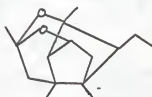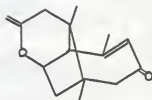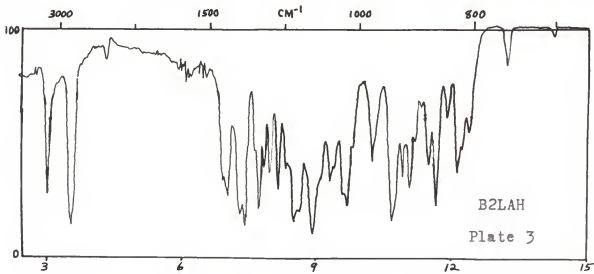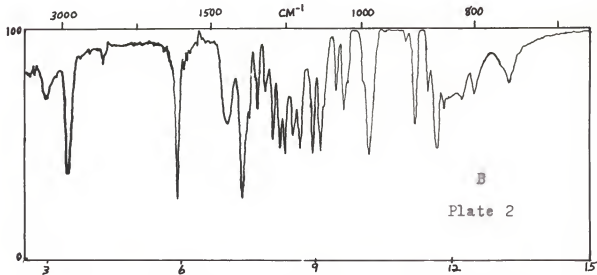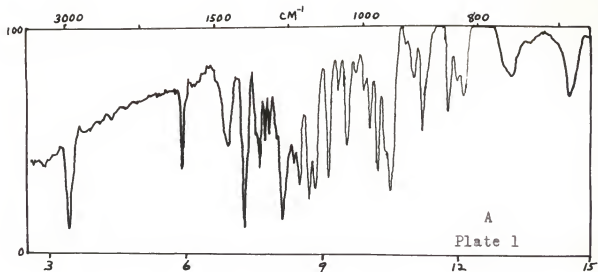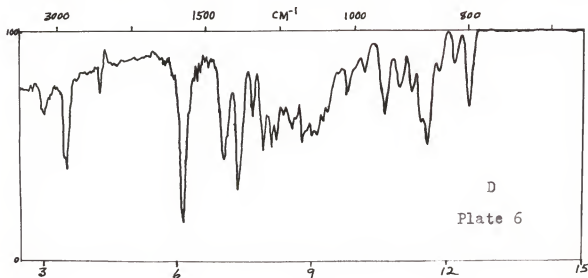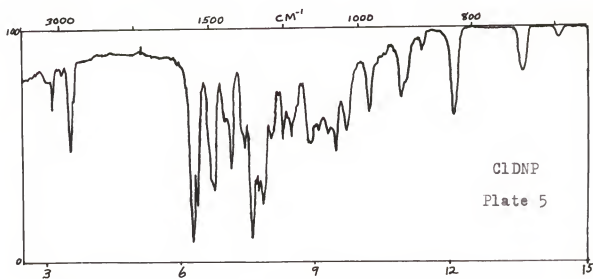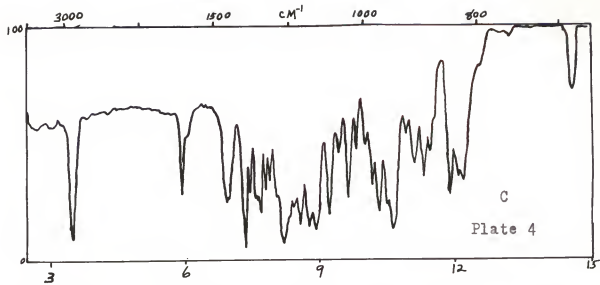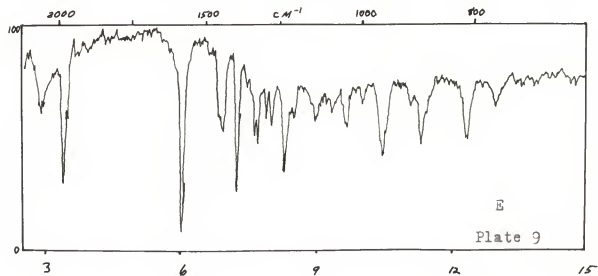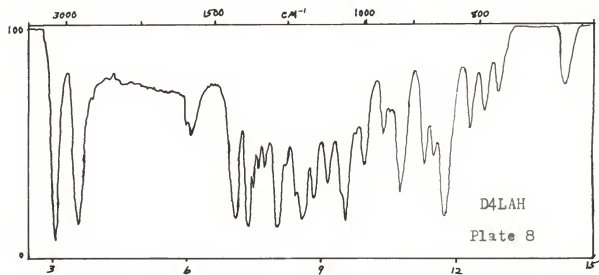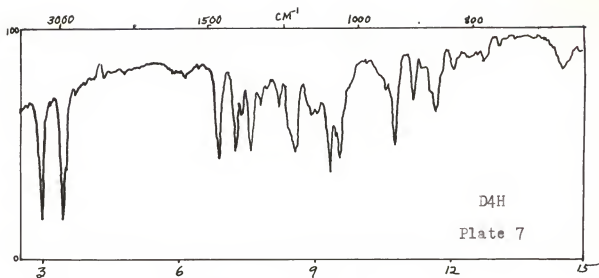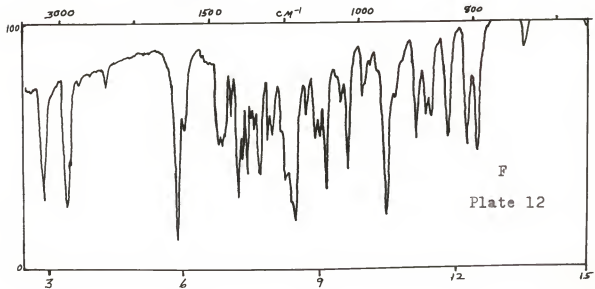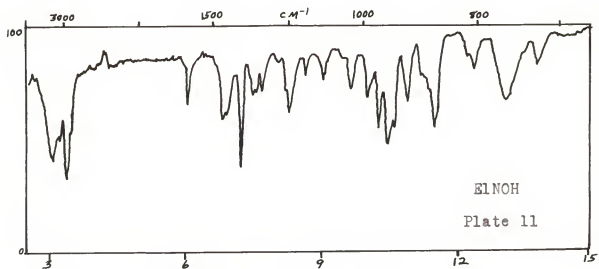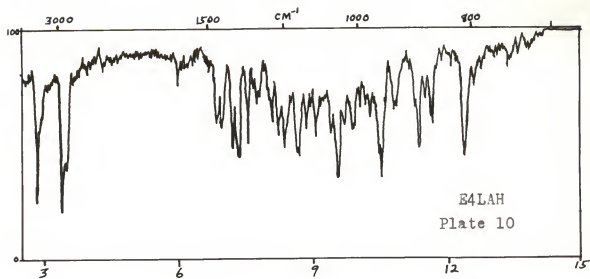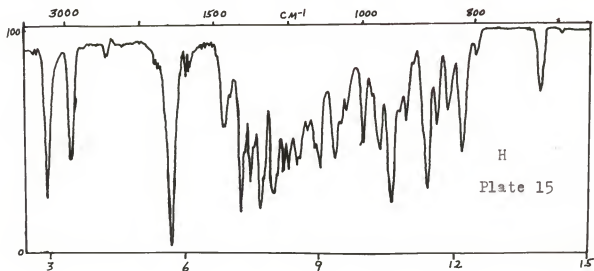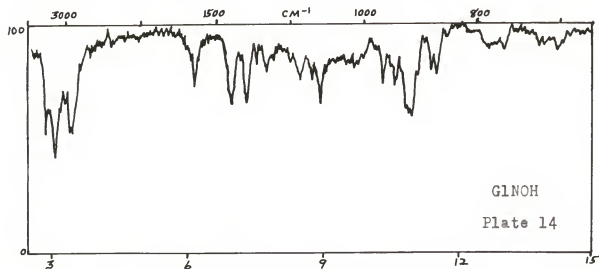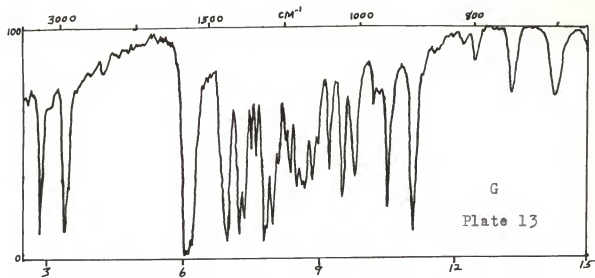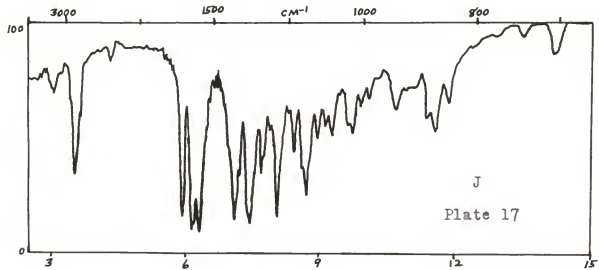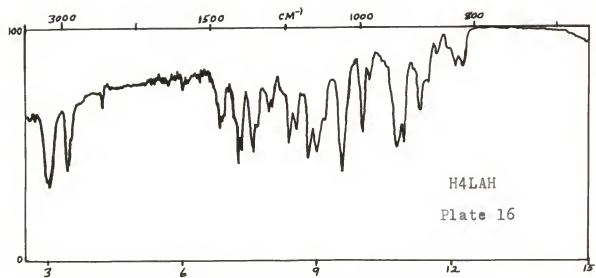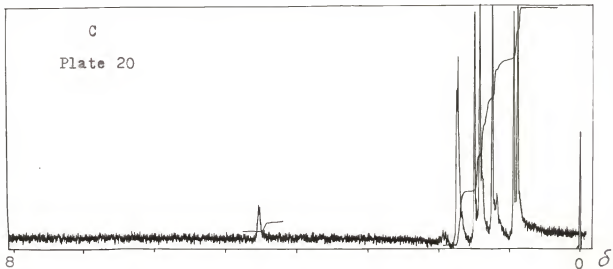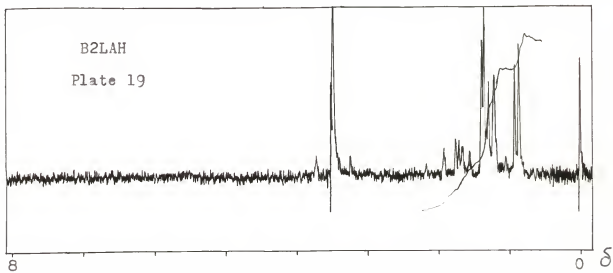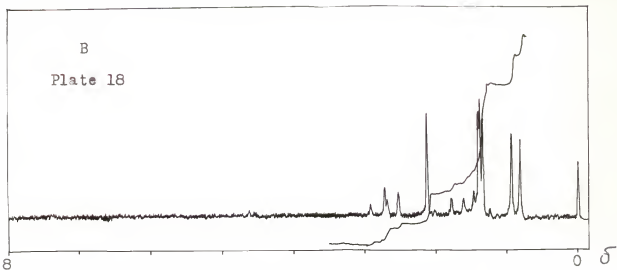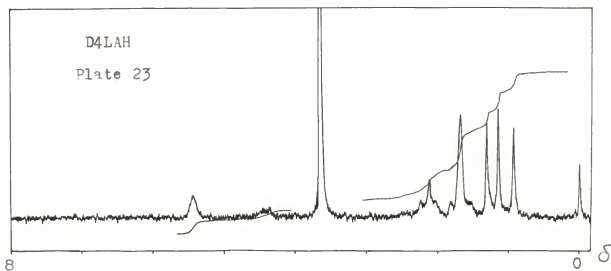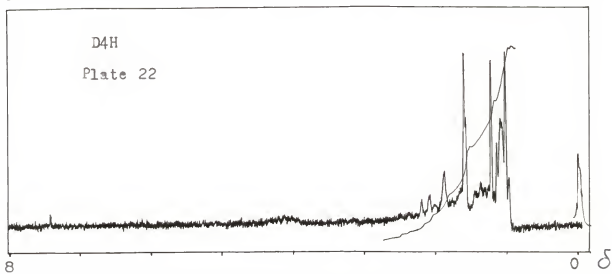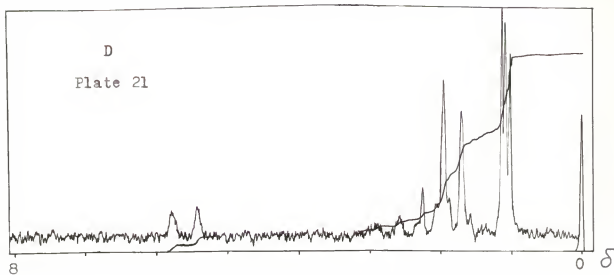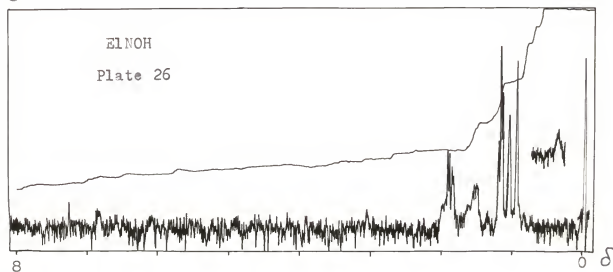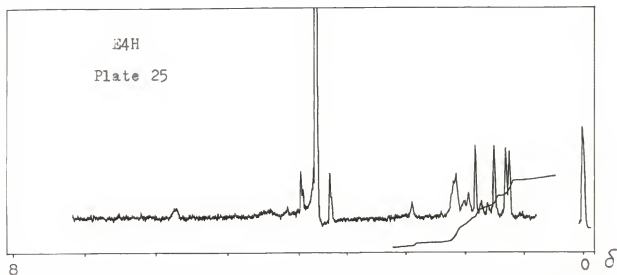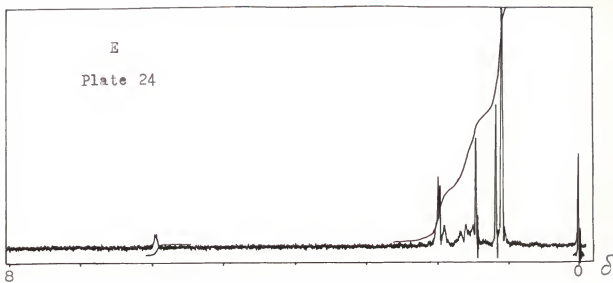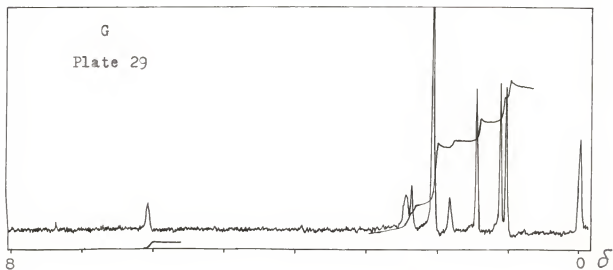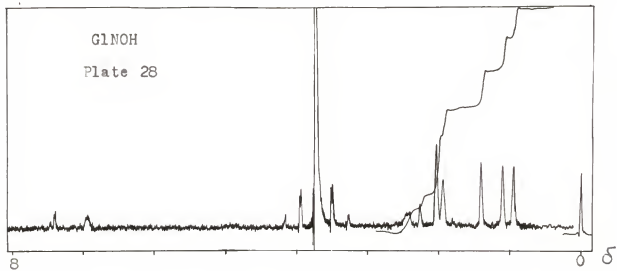
A
Plate 1

B
Plate 2

B2LAH
Plate 3

C

Plate 4

ClDNP

Plate 5

D

Plate 6

D4H

Plate 7

D4LAH

Plate 8

E

Plate 9

E4LAH
Plate 10

E1NOH
Plate 11

F
Plate 12

G

Plate 13

G1NOH

Plate 14

H

Plate 15

H4LAH

Plate 16

J

Plate 17

B
Plate 18

8   0 δ

B2LAH
Plate 19

8   0 δ

C
Plate 20

8   0 δ

D
Plate 21

D4H
Plate 22

D4LAH
Plate 23

E
Plate 24

8   0 δ

E4H
Plate 25

8   0 δ

E1NOH
Plate 26

8   0 δ

F
Plate 27

8   0 δ

GlNOH
Plate 28

8   0 δ

G
Plate 29

8   0 δ

H
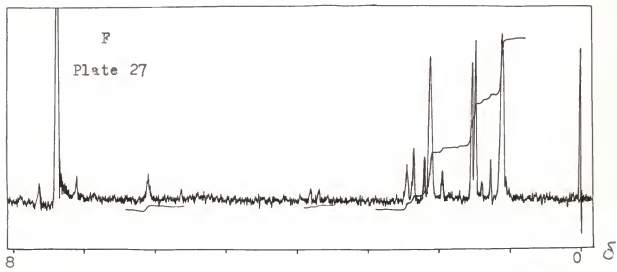
Plate 30

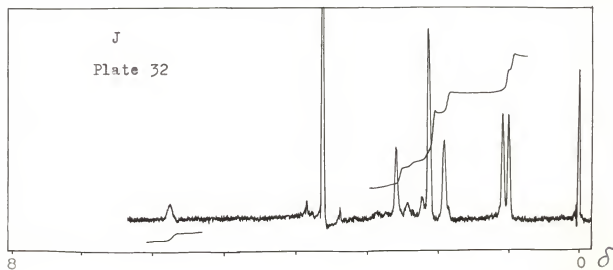8   0 δ

H4LAH

Plate 31

8   0 δ

J

Plate 32

8   0 δ
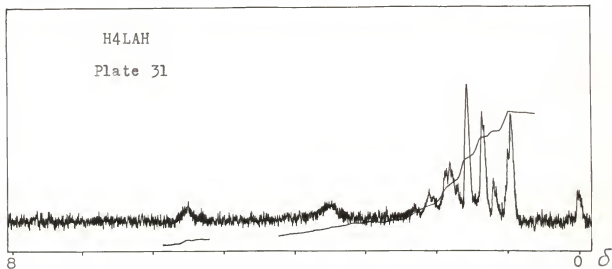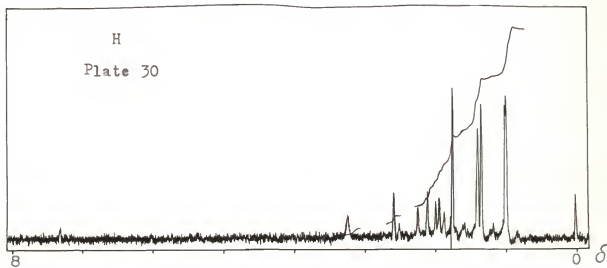
REARRANGEMENT PRODUCTS OF
2,2',4,4',6,6'-HEXAMETHYL-4,4'-BI-4H-PYRAN

by

DAVID H. F. HONIG

B. S., Bethany College, Lindsborg, Kansas, 1962

————————————

AN ABSTRACT OF A MASTER'S THESIS

submitted in partial fulfillment of the

requirements for the degree

MASTER OF SCIENCE

Department of Chemistry

KANSAS STATE UNIVERSITY
Manhattan, Kansas

1965

The purpose of this investigation was to further isolate the products from the mild acid hydrolysis of the title compound, and then by use of spectra, preparation of derivatives and other reactions to establish the structure of these products.

The hydrolysis of the bipyran would be expected initially to produce a tetraketone. Since over 600 structures can be drawn of products which might be expected to form from the tetraketone under the conditions of the hydrolysis, or later treatment with base, a classified catalogue of these structures has been made[1a], and used as the source for possible structures considered in this work.

Five products, designated as A, B, C, D, and E have been previously isolated[1,1a]. Further information has been gained on all of these except A, which has not been isolated pure in this work. However, comparison of spectra indicates that it may be impure C. Four more products F, G, H, and J have been isolated in this investigation.

The original hydrolysis method[1] of treating the bipyran with dilute perchloric acid for an extended period of time, has been the main one used, and has yielded seven of the products. Some improvements have been made in the hydrolysis and in the chromatography, so that yields of up to 50% of crystalline product have been obtained.

Another method[2], involving refluxing for an hour with .34 N HCl solution, has been used once and yielded one different product J, along with E and G. This method seemed to produce fewer products in comparable yield, and with less difficulty in separation.

Compound D, $C_{16}H_{22}O_2$, m.p. 144-145, $\lambda_{max}^{95\% \text{ EtOH}}$ 238 mμ ($\mathcal{E}$ -9500), has yielded more information toward a tentative structure than any of the

other hydrolysis products. The best yield of this product was approximately 6%. A lithium aluminum hydride reduction product, D4LAH, $C_{16}H_{26}O_2$, m.p. 134°, and a catalytic reduction product, D4H, $C_{16}H_{26}O_2$, m.p. 135°, have been produced from D. The analyses, spectra, and chemical reactions of D and its reduction products support the structure shown below, although there are some inconsistencies in the spectral data which have not been fully explained, and more information would be needed to prove a structure. It would be formed from the bipyran by the steps shown.

Bipyran   D
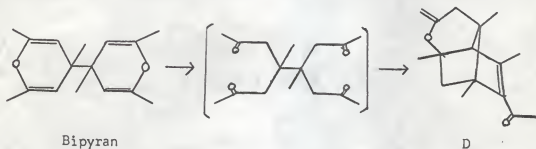
Compound G, $C_{16}H_{22}O_2$, m.p. 145°, is another compound for which a fairly reasonable structure can be proposed. A diconjugated hydroxy tricyclic ketone such as the one shown below fits the chemical and most of the spectral evidence fairly well. Some inconsistencies in spectral data may be due to the overall structure, especially ring strain. The best yield of G, was about 6%. It forms a monoxime, $C_{16}H_{23}NO_2$, m.p. 174° in 90% yield. G would be formed from the bipyran, as shown below.

Bipyran   G
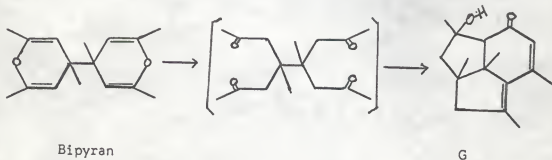
The other compounds isolated are summarized below, as to structure

type, derivative obtained, and approximate best yield from any one hydrolysis.

B, $C_{16}H_{24}O_3$, m.p. 143-144, is a dioxapolycyclic monoketone, optimum yield 8%. It yields a lithium aluminum hydride reduction product, $C_{16}H_{26}O_3$, m.p. 85°.

C, $C_{16}H_{24}O_3$, m.p. 82-83.5°, is a dioxapolycyclic monoketone, optimum yield 11%. A 2,4-dinitrophenylhydrazone, $C_{22}H_{28}N_4O_6$, m.p. 182-184°, has been produced from C.

E, $C_{16}H_{22}O_2$, m.p. 99-100°, is a diconjugated oxapolycyclic ketone, optimum yield 8%. It forms an oxime, $C_{16}H_{23}NO_2$, m.p. 190°, and a lithium aluminum hydride reduction product, $C_{16}H_{26}O_2$, m.p. 151°.

F, no analysis, m.p. 183°, is a conjugated hydroxy ketone, optimum yield 5%.

H, $C_{15}H_{22}O_4$, m.p. 186°, is an unconjugated hydroxy ketone, optimum yield 3%.

J, $C_{16}H_{22}O_2$, m.p. 95°, is a diconjugated ketone. Optimum yield 3%.

An effort to produce 2,2',6,6'-tetraphenyl-4,4'-dimethyl-bi-4H-pyran from 2,4-diphenyl-4-methylpyrilium perchlorate, was unsuccessful.