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The cyclization of a diazoketone with boron trifluoride etherate

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THE CYCLIZATION OF A DIAZOKETONE
WITH BORON TRIFLUORIDE ETHERATE

by


Stephen Joseph Isser UC 1965
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Senior Thesis Submitted
in Partial Fulfillment
of the Requirements of Graduation

DEPARTMENT OF CHEMISTRY

UNION COLLEGE

MAY 1965



ACKNOWLEDGMENT

I would like to express my gratitude for his advice, enthusiasm, and encouragement to Dr. H. E. Sheffer, without whose ever-present guiding eye and understanding, the work summarized here would have been severely hindered.

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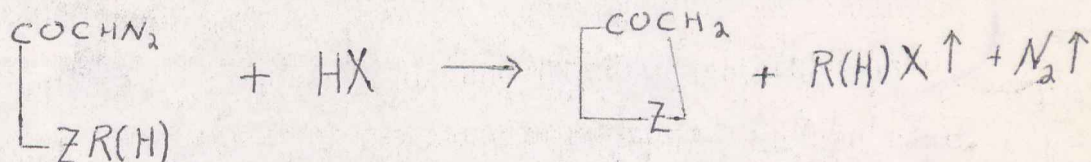
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INTRODUCTION

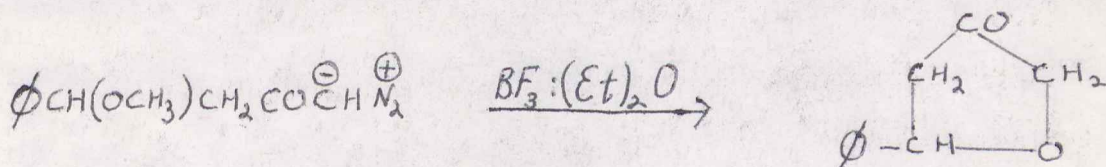
Normally, a diazoketone reacts with an acid to form a substituted methyl ketone.



When a nucleophilic center is present at an α or β position of R, this reaction may lead to the formation of a cyclic ketone (11).



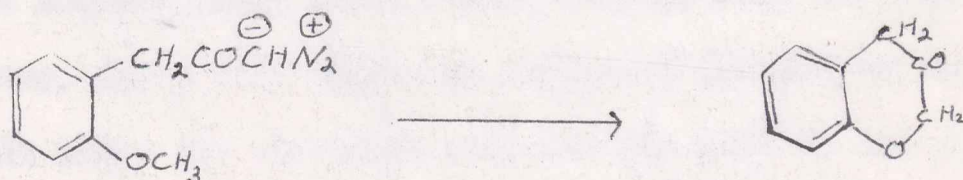
It was the purpose of this research to investigate the cyclization of the aliphatic methoxydiazoketone, 1-diazo-4-methoxy-4-phenyl-2-butanone (I), when treated with BF_3 in ether, to give the five-membered ring 5-phenyltetrahydrofuranone-3 (II).



(I)

(II)

Cyclic products from diazoketones have been obtained in the aromatic series with systems having ortho-substituents. Moore and Sheffer (11), at the University of Delaware, reacted 1-diazo-3- (o-anisyl) -2-propanone (III) with acids whose anions varied greatly in their nucleophilic strength, in an attempt to prepare 3-chromanone (IV).



(III)

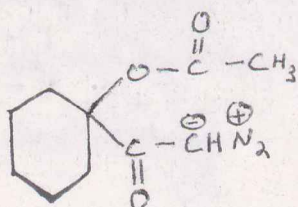
(IV)

The reaction was carried out using acetic acid, sulfuric acid, a catalytic amount of sulfuric acid, and finally boron trifluoride etherate. The acetate ion is a strong nucleophile, so that in solution it attacks the α carbon quite readily to form the open chain substituted acetate. The cyclization which presumably proceeds through the much weaker nucleophile (ortho attached methoxy oxygen) cannot compete with the powerful acetate ion, and the absence experimentally of any ring product verifies this theory. Bisulphate ion is a slightly weaker nucleophile than acetate ion, but still

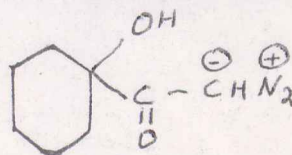
more powerful than the methoxy group, so that a trace of ring formation is observed while the predominant product is the open chain bisulfate. The use of only a catalytic amount of sulfuric acid allows ring formation since the concentration in solution of the methoxy group is much higher than the bisulfate and there is a greater probability that although the methoxy group still cannot compete with the bisulfate group, there will be enough unreacted diazoketone molecules left after the bisulfate radicals are used up for ring formation to occur under the catalytic action of the hydronium ions. An increased yield of the cyclic product was subsequently noted. Boron trifluoride is a Lewis acid (an electron pair acceptor) and has no nucleophilic properties whatsoever. Yet it was found to catalyze the reaction and since much of the competition is now eliminated, the yield should be virtually all ring product. This indeed was found to be the case and based on these results, BF_3 was chosen for the reaction of (I).

In the aliphatic series, more difficulty has been encountered than in the aromatic series due, not to differences in mechanisms of reactions but primarily to the problems of obtaining crystalline derivatives with these

usually low molecular weight diazoketones. Diazoketones such as (V) and (VI) showed a pronounced tendency to form four-membered rings upon treatment with even mineral acids (9).

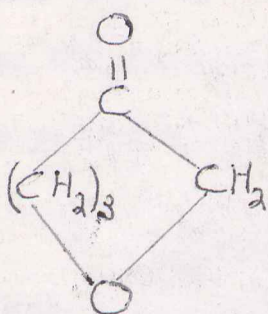


(V)

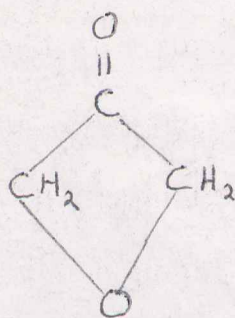


(VI)

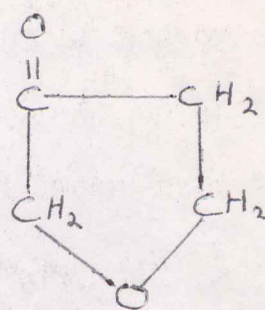
No open chain products were isolated in the latter case even in the presence of excess nucleophile (X^-). Thielking (13) attempted the preparation of (VII) and Hoster (5) tried oxetanone-3 (VIII) and tetrahydro-3-furanone (IX), all using BF_3 as the cyclizing agent.



(VII)



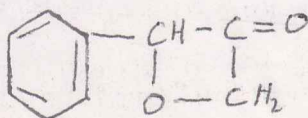
(VIII)



(IX)

These syntheses were largely unsuccessful for a myriad of

reasons, but substantial evidence for the expected by-products of the reaction (the fluoroketone, the hydroxyketone, and the ethoxyketone) was found. Kagan (6) attempted a four-membered ring synthesis, the phenyl group being attached to the α' carbon to increase the probability of forming crystalline derivatives.



(X)

The results of this work were inconclusive as one of the products in the synthesis of the diazoketone (the acid chloride) decomposed unbeknownst to the author, at the time. Belli (3) began the work with (I) in 1963 and, due to the same difficulties that Kagan encountered, was unable to prove the presence of the ring structure.

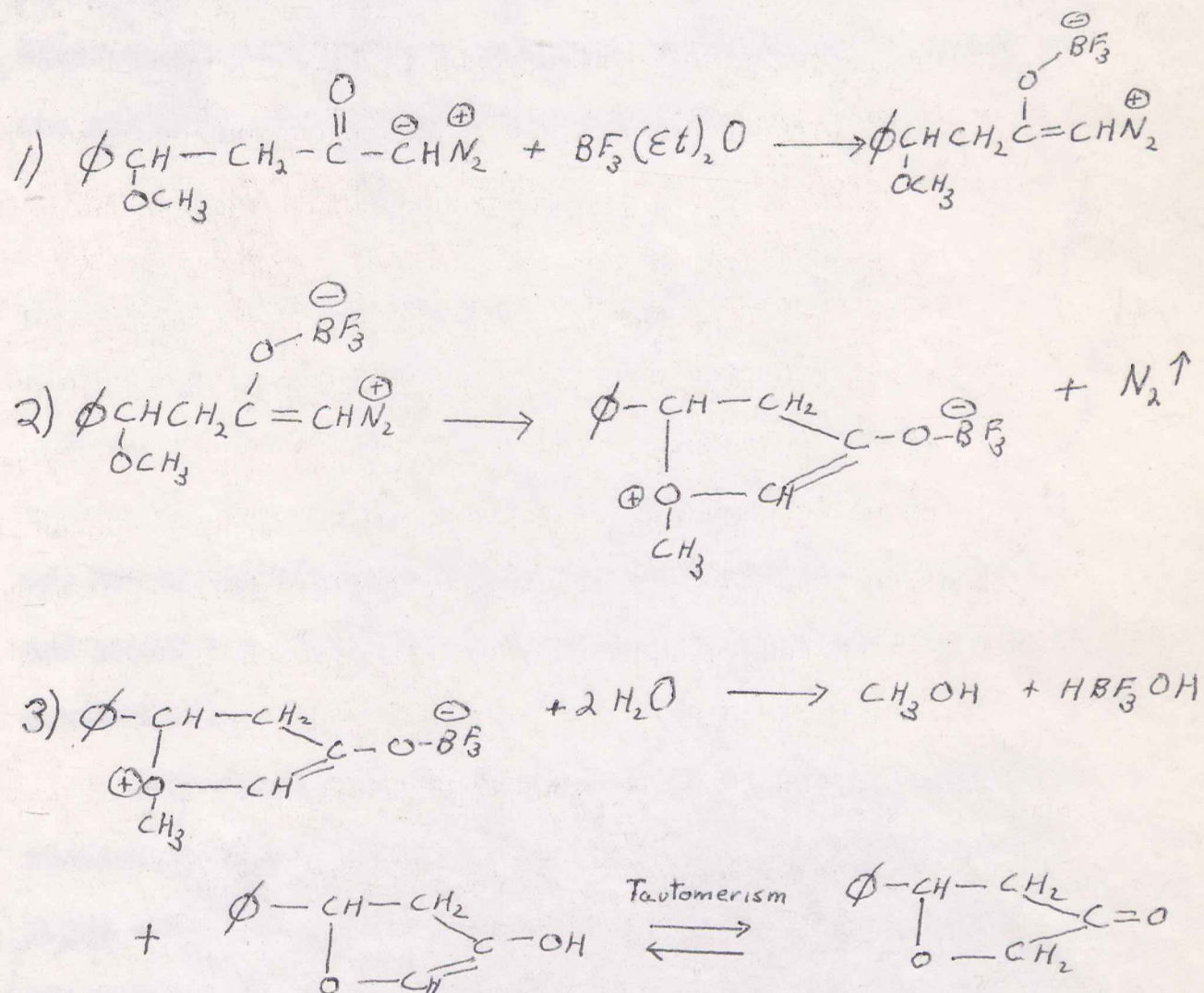
It should be mentioned here that because of ring-strain, five-membered rings (II) are easier and more likely to be formed than four-membered rings (VIII).

The boron trifluoride cyclization reaction has become important lately in the synthesis of drugs and hormones;

especially those containing an aromatic ring incorporated in a steroid system.

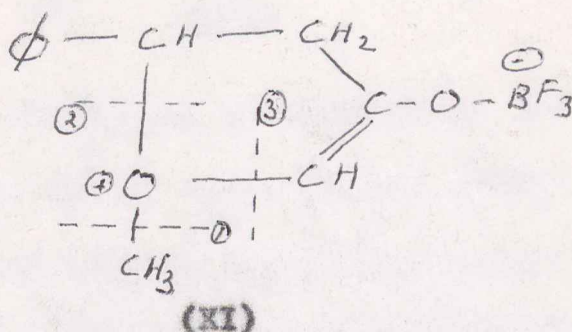
Careful studies, primarily the work of Dr. Sheffer, have led to the following proposed mechanism of the reaction:

(I) \longrightarrow (II).



It involves the formation of an oxonium fluoroborate ion followed by nucleophilic attack at the methyl group.

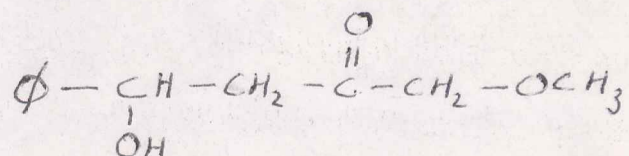
It is also thought that the initial step may be BF_3 attack at the methoxy oxygen instead of the carbonyl oxygen, although the subsequent mechanism is quite similar. Further, since the reaction to the stable ring product involves two steps (the addition of the diazoketone to the $\text{BF}_3 \cdot (\text{Et})_2\text{O}$ and after completion of this reaction, the addition of water to the mixture), the reaction intermediate



may be relatively long-lived, and thus efforts to capture and prove its structure by infra-red spectroscopy have been carried out.

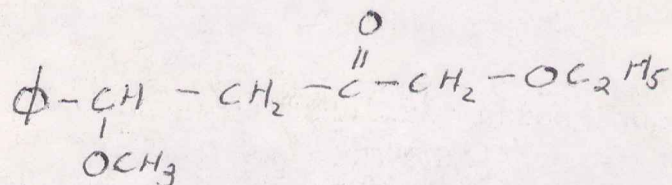
Although there are no particularly strong nucleophiles present in the reaction mixture besides the methoxy group, there are more than one, and all of approximately equal strengths. These nucleophiles compete with the cyclization reaction and the amount of each product obtained is a measure of the relative strengths of the competing nucleophiles. The intermediate (XI) may split off a methyl group ① forming

the desired 5-phenyltetrahydrofuranone-3 according to the mechanism. This is most likely. Next in probability, the methoxy group may detach itself from the α' carbon (2) and form the open chain methoxy ketone (XII).



(XII)

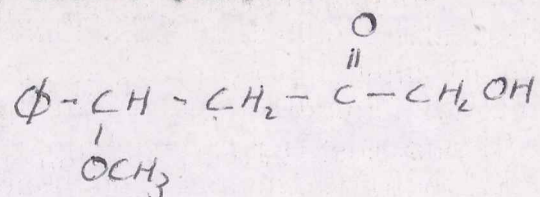
Of about the same likelihood as the methoxy open chain product would be an ethoxy chain product (XIII) formed by cleavage of the bond between the methoxy oxygen and the carbon adjacent to the ketone function (3) with the subsequent nucleophilic attack by diethyl ether, present as the solvent.



(XIII)

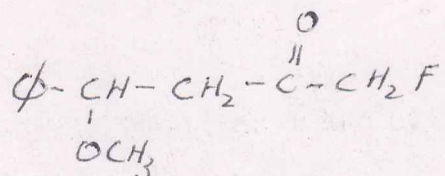
On addition of water to the intermediate (XI), hydrolysis of the fluoroborate may occur with subsequent ring cleavage to

form the hydroxy ketone (XIV).



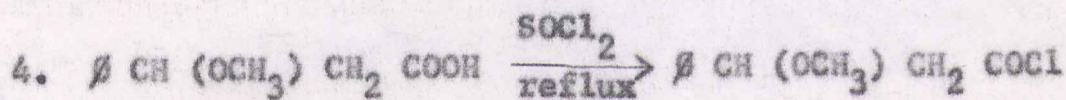
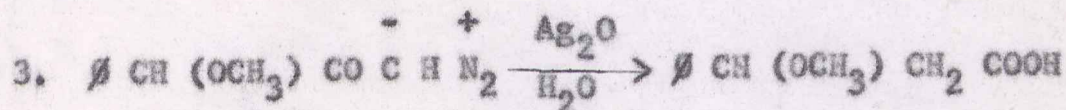
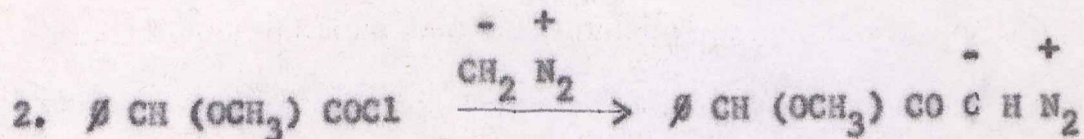
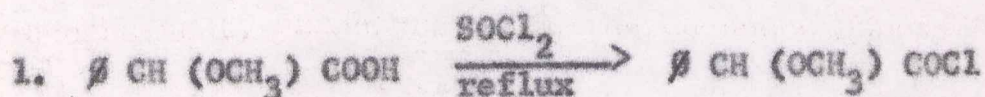
(XIV)

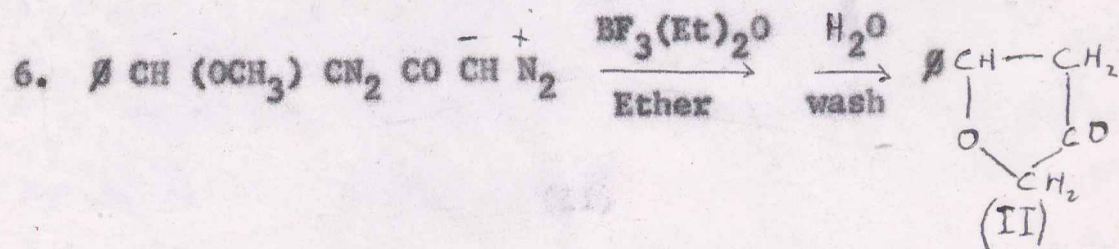
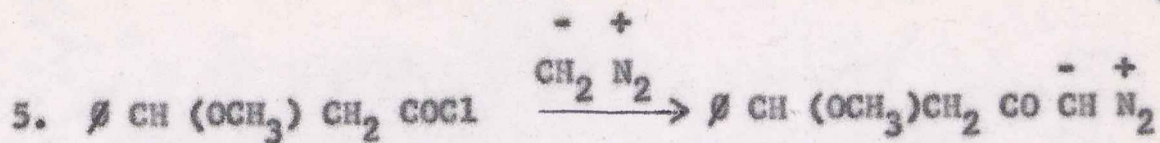
Finally, a fluorine atom can break away from the $-\text{O}-\text{BF}_3$ group and attack the α methyl to form a fluoroketone (XV).



(XV)

The proposed route to the synthesis of (II) starting from α -methoxy-phenylacetic acid is as follows:

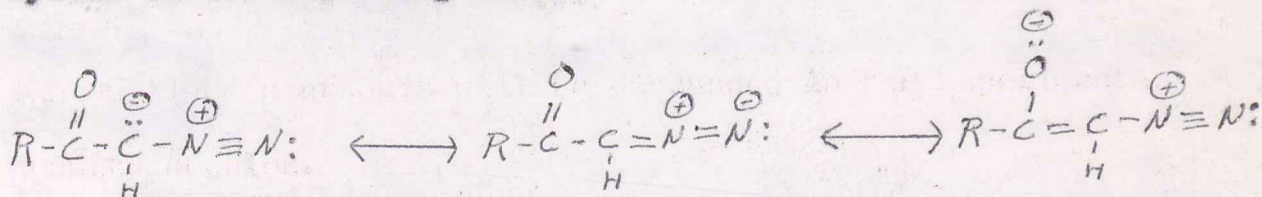




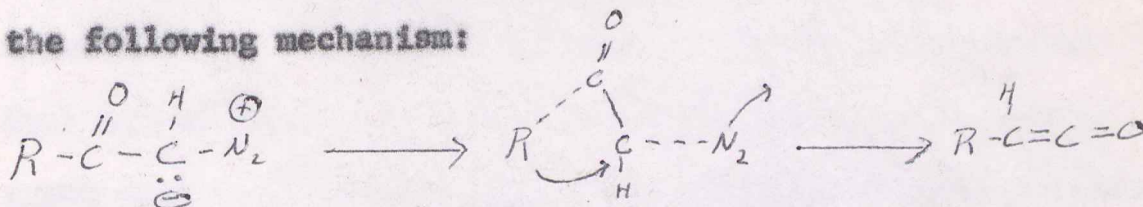
The outlined synthesis will be discussed in the Experimental Results section.

HISTORICAL

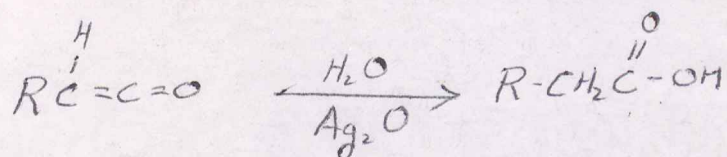
The actual structure of a diazoketone is a resonance hybrid of the following forms:



Diazoketones were discovered at the beginning of the 20th century by the German chemist L. Wolff (15). His studies led to what is now known as the Wolff rearrangement in which a diazoketone is converted to its primary carboxylic acid or ester in the presence of silver ion catalyst. It has the following mechanism:



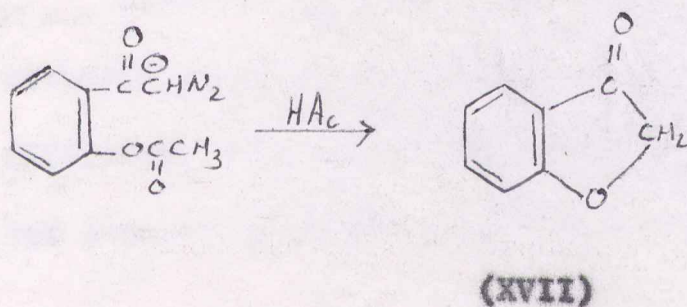
The ketene formed yields the acid upon addition of water:



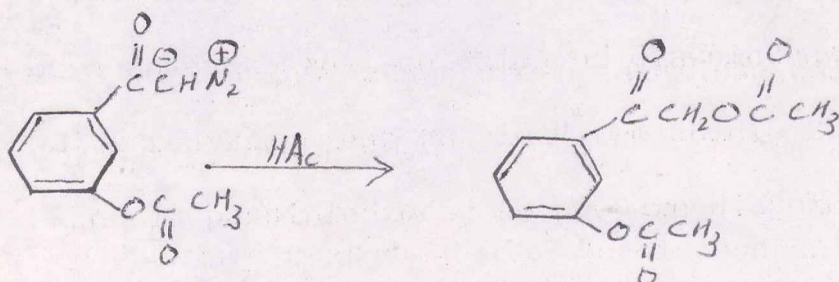
In the late 1930's, Arndt and Eistert (1) developed a

method using diazoketones to convert a carboxylic acid to its next higher homolog. It consisted of converting the acid chloride to the diazoketone by treatment with an excess of a cold ethereal solution of diazomethane and the subsequent Wolff rearrangement to yield the acid. Further investigation makes it possible today to prepare diazoketones in better than 80% yields.

The diazoketones were found to decompose readily at room temperature by evolving nitrogen gas. However, they may be stored, using great care, for a period of one to two weeks at 0-5°C. They are rapidly decomposed in acid to yield substituted methyl ketones as was mentioned before. Exceptions, however, were found among the aromatic diazoketones with appropriate ortho substituents which underwent cyclization reactions in the presence of acids. In 1942, Elderfield, Kuch and Marshall found that α -diazo-*o*-acetylacetophenone (XVI) when treated with glacial acetic acid yielded a cyclic product, coumaranone (XVII) (8)



while reaction of the corresponding meta compound produced α -acetoxy-in-acetoxyl acetophenone (XVIII).

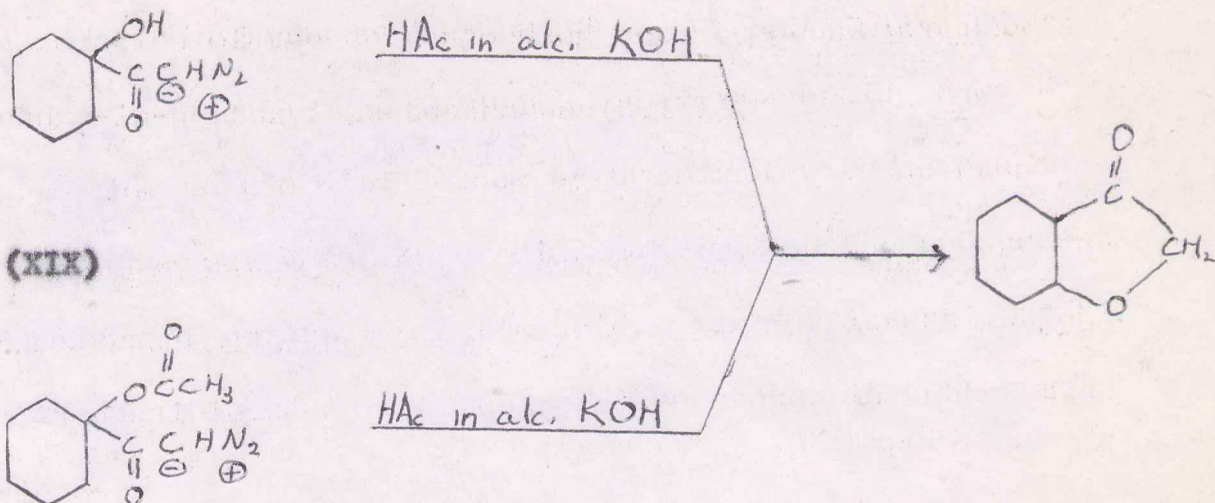


(XVIII)

Ten years later, in 1952, Bose and Yates (4) obtained the same product when they treated diazo-*o*-methoxyacetophenone with a catalytic amount of hydrogen ion to form coumaranone (XVII). They reasoned that only catalytic amounts of acid were required since this proton was recovered when methanol is split off by solvolysis of the oxonium intermediate.

Herman substituted an *o*-hydroxy group for the *o*-methoxy group and in the same reaction still obtained coumaranone.

Marshall and Walker (9) were able to obtain a four-membered heterocyclic ketone, 1-oxaspiro (3,5) nonan -3-one (XXI) from both 1-hydroxyl-1-*w*-diazoaceto cyclohexane (XIX) and 1-acetoxy-1-*w*-diazoaceto cyclohexane (XX).



There is an indication that Marshall and Walker may have prepared oxetanone-3 (VIII) (9) by reacting the diazoketone with glacial acetic acid.

The contribution of Moore and Sheffer (see Introduction) was to advance the theory that relative nucleophilicity is a determining factor in the cyclizations with their work using $\text{BF}_3 \cdot (\text{Et})_2\text{O}$.

APPARATUS

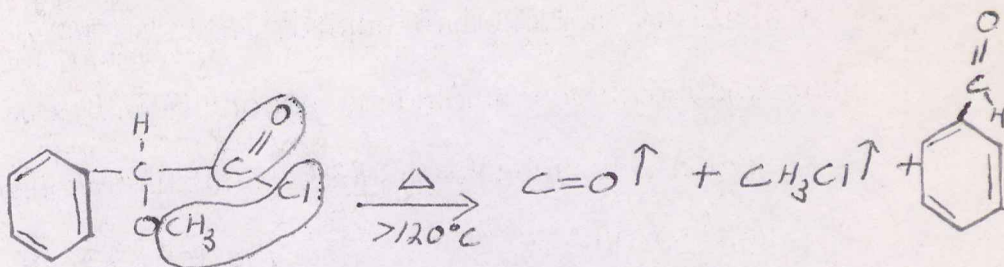
Common laboratory pyrex ground glassware was used throughout the research. Mechanical or magnetic stirrers and heating mantels were used whenever possible over less efficient stirring and heating methods.

Analyses were conducted using the Perkin-Elmer Model 154-L Vaporfractometer equipped with either a silicone, "R," or "A" column; the F and M Scientific Model 720 with a silicone column, the Perkin-Elmer Model 21 Infra-red Recording Spectrophotometer, with NaCl cells, and the Varian Nuclear Magnetic Resonance Spectrometer. The vaporfractometers were used to check the purity of fractions and for fractionally distilling minute quantities, while the infra-red and nuclear magnetic resonance spectrometer were used to determine functional groups present and their arrangement in the compound.

EXPERIMENTAL RESULTS

1. Preparation of α -methoxy-phenyl acetylchloride

Previous workers had failed to prepare this acid chloride using ordinary methods and so the preparation of the chloride was the main stumbling block in the synthesis. Workers previously prepared the acid chloride by refluxing with thionyl chloride and distilling the mixture at air pressure to yield the desired product. In the case of α -methoxy-phenyl acetylchloride, the literature forbids this (2, 12) for it states that this compound will decompose to benzaldehyde, methyl chloride, and carbon monoxide if distilled at a temperature above 120°C .



Since the estimated boiling point is about 175°C . all distillation work should have been done at reduced pressure.

Several test runs were made to determine the optimum conditions for preparation. On several of the runs, products were obtained at distillation temperature close to those estimated for the acid chloride, but when these were subjected to vapor phase analysis, two sharp unknown peaks of equal area and low retention time and a broad symmetrical peak with a retention time corresponding to benzaldehyde were obtained (see Figure 1A). It was reasoned, then, that the presence of the benzaldehyde peak and the absence of a peak for the acid chloride indicated that the desired product had been formed and had rapidly decomposed to benzaldehyde before or during distillation. An infra-red analysis of one of these typical distillation products, however, showed a strong absorption band at 5.65μ which the literature claims, represents the carbonyl function of an acid chloride, and a weak band at 5.875μ which denotes the carbonyl group of benzaldehyde (see Figure 1B). According to a rough analysis there was 75% acid chloride in the distillate and 25% benzaldehyde. Many of the previous runs, then, had been successful in preparing the compound even though we were not sure because v.p.c analysis had indicated benzaldehyde. To account for the lack of an acid chloride peak on vapor phase,

it was hypothesized that although the acid chloride was present before VPC analysis, the high temperature of the injection port ($\sim 200^{\circ}\text{C}.$) and the high temperature for which the column was set ($175^{\circ}\text{C}.$, i.e. $> 120^{\circ}$) combined to decompose the acid chloride upon being injected into the column. The two gases (CO and CH_3Cl) would have very low retention times and be of equal area and the sum of these two areas would be twice the area of the benzaldehyde peak. This was found to be the case (see Figure 1A) and then based on the experience of the several trials the following procedure was formulated and executed.

35.57 g (0.21 Moles) of α -methoxy phenyl acetic acid (Eastman Organic Chemical) were carefully dried for 3-4 days at $50^{\circ}\text{C}.$ 38.44 g (0.32 Moles, i.e. a molar ratio of 1.5:1 with the acid) of pure thionyl chloride were added to a three-necked flask to which a mechanical stirrer (magnetic stirrer would be better), condenser, and adapter for vacuum distillation were attached. A drop of pyridine was added and the SOCl_2 warmed for a short time below its boiling point ($\sim 80^{\circ}\text{C}.$). The acid was added in small portions over a period of $2\frac{1}{2}$ hours in which the mixture was constantly stirred but not heated.

The reaction could be seen to be taking place. In order

to keep the system free from moisture, as acid chlorides hydrolyze readily, calcium chloride tubes were attached to all open orifices. Bubbling nitrogen through the system was found by MacKinnon (7) to be even more effective. After refluxing, the mixture was vacuum distilled at 0.5 - 0.7 mm. and two light yellow colored liquid fractions (10-1 and 10-2) of acid chloride were collected (B.P. 76-85^o). These were combined to yield 32.04 g (0.175 Moles) of product, an 82% yield. An additional 0.359 Moles of product (11-1) were prepared by a similar procedure except that the mixture was allowed to reflux over night. The total amount of acid chloride prepared was 0.534 Moles. The purity was about 85% by IR analysis.

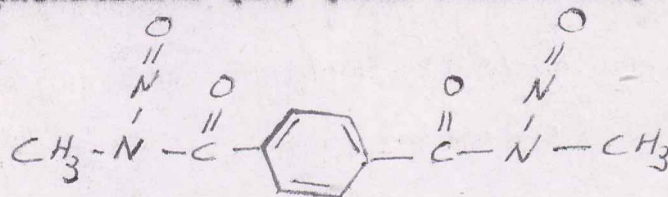
2. Preparation of β -Methoxy- β -phenyl-propionic acid

A. Preparation of Diazomethane

Diazomethane was prepared according to the procedure described by Reed and Moore (10).

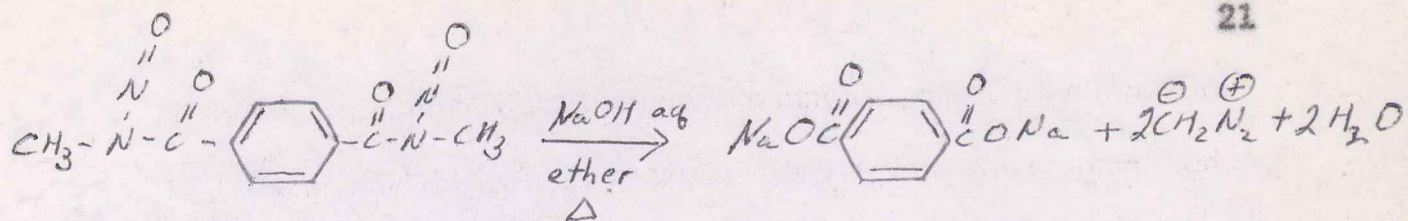
In a 5-liter round, 3-necked flask were placed 3000 ml. of ether, 450 ml. of diethylene glycol monoethyl ether (Matheson, Coleman and Bell), and 600 ml. of 30% aqueous NaOH solution. The mixture was chilled

in an ice-sodium chloride bath to 0°C. and finally 125 g (0.5 Mole) of bis-(N-methyl-N-Nitroso) terephthalimide (XX) (E.I. DuPont Co.)



(XX)

were added in portions. The flask was immediately transferred to a heating mantel and connected by a goose-neck to a 60-cm condenser connected to a receiving flask. The pressure built up inside the receiving flask during distillation was controlled by equalizing the pressure with a stopcock. Enough absolute ether was placed in the receiving flask to cover the tip of the adapter in order to minimize the loss of diazomethane (a gas). The yellow color of diazomethane appeared almost immediately in the receiver and about 2 liters of ether-diazomethane were distilled in one hour. The reaction ends when the yellow color is no longer present in the distilling flask. The reaction is:

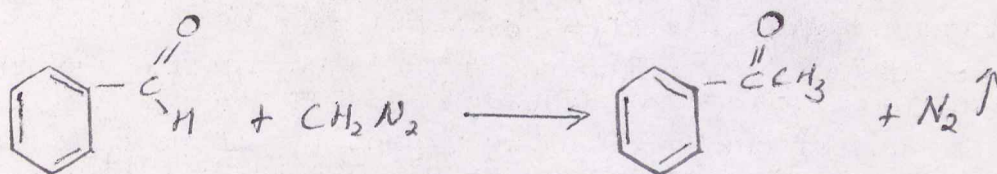


The entire reaction was carried out in a ventilated hood, and great care was exercised in handling the highly toxic diazomethane. A theoretical yield of 1.0 Moles of diazomethane was to be obtained from the starting material, while the actual yield in this reaction is usually 80-90% (5). Two 0.8 Mole batches of diazomethane were so prepared. Without any further treatment, the diazomethane is ready for the preparation of the diazoketone.

B. Preparation of 1-Diazo-3-methoxy-3-phenyl-2-propanone

To each batch of fully prepared diazomethane in ether was added 0.23 Moles of α -Methoxyphenyl acetyl chloride diluted with about 10-20 ml. of absolute ether. After about two minutes, gas evolution was observed (CH_3Cl) and seen to continue for over an hour at which point the flasks were stoppered with one hole rubber stoppers each mounted with a calcium chloride tube and

allowed to stand overnight in the hood to make sure that all the diazomethane was gone. The next day the reaction mixture was filtered to get rid of the polyethylene formed, and finally the ether was evaporated under reduced pressure. No heat was applied in order to prevent decomposition of the rather unstable diazoketone, although occasionally a lukewarm water bath was used to remove the ice formed on the outside of the flask. It took about six hours to completely evaporate the ether. About 83.6 g (0.44 Moles) of the diazoketone, a brown-colored viscous oil, were obtained (12-1). The yield was 94.5% based on nitrogen volume measurements of step C; the actual product was not weighed. Infra-red analysis (see Figure 2) indicated a diazoketone peak at 4.78μ and the shifted C-O group at 6.15μ . A very weak carbonyl band at 5.93μ probably indicates the presence of the ketone, acetophenone, an expected impurity in the reaction of diazomethane with the acid chloride impurity benzaldehyde.



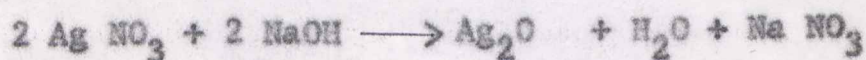
The mixture is about 98% pure based on an IR peak analysis.

C. Preparation of β -methoxy- β -phenyl-propionic acid
(The Arndt-Eistert Synthesis)

The β -methoxy- β -phenyl propionic acid preparation was carried out according to the method described in (1) and (10).

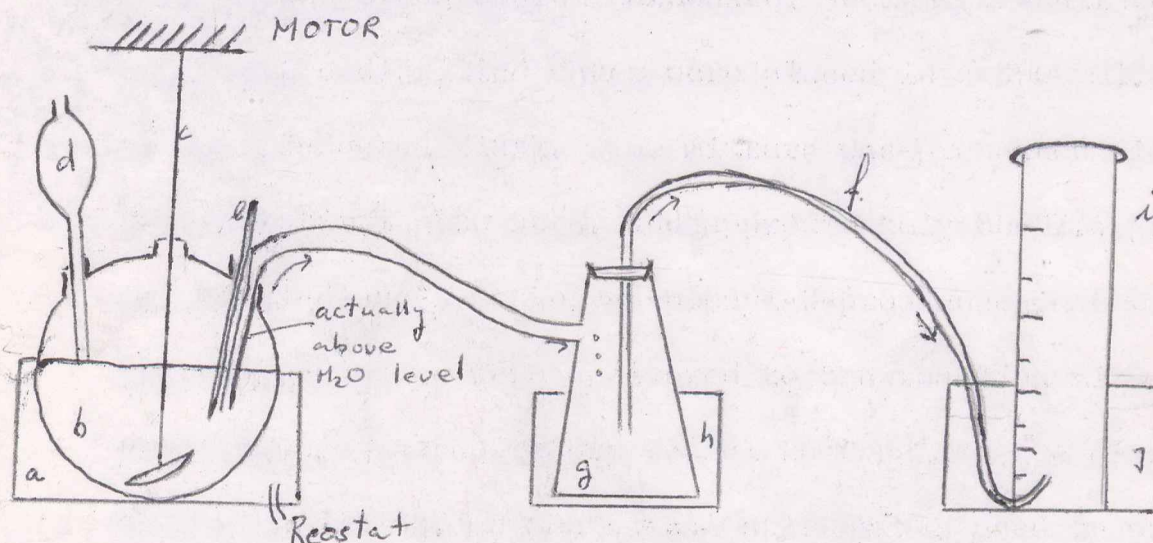
<u>Reagent</u>	<u>Grams</u>	<u>Moles</u>	<u>Rel. Amounts</u>
Diazoketone	87.4 (Theoret.)	0.46 (Theoret.)	1
p-Dioxane (pure)	608	6.9	15
Silver oxide	11.73	0.0506	0.11
Sodium Carbonate	30.2 (anhy.)	0.62	0.285
Sodium Thiosulfate	18.17 (dry)	0.115	0.25
Water (distilled)	1184	65.78	143

Silver oxide (Ag_2O), the catalyst, was prepared by adding 40 ml. of 10% NaOH solution to 173 ml. of 10% Ag NO_3 solution, being careful to avoid excess of hydroxyl ion.



The solution was washed ten times with distilled

water, filtered by suction and the brown precipitate washed 10 more times with water. The silver oxide, anhydrous sodium carbonate, sodium thiosulfate, and the distilled water were placed in a 3000 ml. round 3-necked flask. The mixture was preheated with stirring to 50°C. and approximately 80-87.4 grams of 1-diazo-3-methoxy-3-phenyl-2-propanone in 608 ml. of p-dioxane were delivered to the reaction mixture by using a separatory funnel to regulate the diazoketone addition. A mechanical stirrer was used to provide constant and thorough mixing, and a heating mantle supplied heat to the reaction mixture. The nitrogen evolved was collected in 1 liter graduated cylinders by displacement of water, a trap being used between the reaction flask and the cylinder to prevent the water from entering the flask. The apparatus assembly is shown on page 25.



- a. Heating mantle
- b. Reaction flask
- c. Mechanical stirrer
- d. 125 ml. separatory funnel
- e. Thermometer
- f. Tubing
- g. Trap
- h. Ice bath in order to condense any vapor that might escape from the reaction flask
- i. Graduated cylinder to measure the N_2 evolved
- j. Trough

Rapid and immediate evolution of nitrogen was noted upon the first additions of the diazoketone. The evolution was not regular, but in spurts. The evolution slowed down after a short time due to the decreasing efficiency of the catalyst, so the bath temperature was raised slightly to restore the evolution rate and raised again each time the evolution rate was found to be low; at the end of the reaction the bath temperature was 90-100°C. It should not be raised above this temperature. When increasing the temperature was not sufficient to keep the nitrogen evolution going, fresh amounts of catalyst were added and a reaction rate increase was noted. Within a period of several hours of reaction time, 10.25 liters of nitrogen were collected. By the ideal gas law ($pV = nRT$), for a theoretical diazoketone yield of 0.46 Moles, 10.83 liters should be collected. The volume actually collected represented a 94.5% yield of diazoketone (see previous step). The dark brown-greenish colored reaction mixture was allowed to stand overnight. At this point, it is recommended that in future work, after the mixture has been diluted with water and gravity filtered, the basic solution be filtered through alumina (1). This will remove traces of colloidal silver or silver salts which may

have been formed during the reaction. The alkaline solution was extracted five times with small portions of solvent ether. These extracts were discarded. The clear aqueous solution was carefully acidified with 20% HCl to pH 1 and saturated with technical NaCl. The separation of two layers was observed, yellow oil at the top and almost clear solution at the bottom. The solution was extracted five times with ether and the ether extracts united and extracted seven times with a 10% NaOH solution (separation of the organic acid from the sulfur precipitated by the action of HCl on $\text{Na}_2\text{S}_2\text{O}_3$). The sodium hydroxide extracts were yellow. The united NaOH extracts were acidified with 20% NaOH, saturated with technical NaCl, and extracted with ether as before. The united ether extracts were washed with activated charcoal to remove colored impurities, filtered through Na_2SO_4 to remove water, and evaporated under pressure. The crude product was a dark brown oil and some yellowish crystals. Ligroin (B.P. 100°C .) dissolved the crystals but not the oil, and large white crystals of the acid were obtained on recrystallization from the ligroin solution (15-1). This fraction weighed 10.93 grams and had a melting point of $92-93.5^\circ\text{C}$. The pure acid melts at 98°C . Recrystallization of the mother liquor and

attempts at obtaining acid from the oily residue (by dissolving in ether and recrystallizing with ligroin) finally yielded two rather more impure crystal fractions (15-2 and 15-3) which were light brown in color and which melted (after several recrystallizations) at 87-95°C. Their combined weight was 19.84 g and thus the overall acid yield was 30.77 g (0.17 Moles) and based on the actual diazoketone yield (0.44 Moles) represents a 38.6% yield. Infra-red analysis of an acid sample shows a strong carbonyl peak at 5.863 μ (within the wavelength region ascribed to saturated carboxylic acids), and a weak band at 6.15 μ which is evidently a vestige of some unreacted diazoketone in the solution. (see Figure 3). Neutralization equivalent analysis (titration with aqueous NaOH) of a sample of 15-2 and 15-3 combined, showed a purity of 94.4%.

3. Preparation of β -Methoxy- β -phenylpropionyl chloride

The procedure used for the preparation of β -methoxy- β -phenyl propionyl chloride was the same as that for α -methoxy phenyl acetyl chloride. 18.5 grams (0.103 Moles) of acid prepared in 2.C. was added in

portions to 200 grams (0.168 Moles) of SOCl_2 preheated with a drop of pyridine. (Note that the pure and impure acid fractions were mixed.) Two fractions were obtained:

16-1 - light yellow tinged liquid B.P. $124^\circ/5$ mm

16-2 - dark yellow colored liquid B.P. $\sim 130^\circ$.

1.59 grams (0.008 Moles) of the very pure 16-1 and 3.97 grams (0.02 Moles) of the impure 16-2 which was redistilled several times in an attempt to purify it, were collected. The total yield was a poor 36.8%. It was apparent that an error in judgment had been committed here. Since β -methoxy- β -phenyl propionyl chloride is expected to be very stable (the methoxy and phenyl group being attached to a β -carbon, one removed from the reactive alpha site). A more vigorous method of preparation is called for. The non-heated refluxing used for the first acid chloride does not adequately satisfy the requirements evidently demanded for preparation of the stable acid chloride. In a later attempt to prepare more and purer acid chloride, 8.87 grams (0.045 Moles) of β -methoxy- β -phenyl-propionic acid was added in portions to 7.41 grams (0.068 Moles) of

preheated SOCl_2 and the mixture heated while stirring for at least one hour. The dark colored reaction mixture was vacuum distilled at 12 mm and one fraction (19-1) of slightly yellowish acid chloride boiling at $125-135^\circ\text{C}$. was collected. About 4 g (0.02 Moles) were collected, representing a 44.8% yield, a significant increase over the previous method. It is thought that prolonged heating will increase the yield even more. Technical difficulties were encountered in all the distillations of this product due to severe uncontrollable bumping which often carried crude product into the receiving flask. Infra-red analysis showed the typical acid chloride carbonyl band (see 1.A). Due to the malfunctioning of the gas chromatographer, no analysis for purity was carried out although it is estimated that both acid chloride fractions were more than 80% pure.

4. Preparation of 1-diazo-4-methoxy-4-phenyl-butanone-2

0.02 Moles of β -methoxy- β -phenyl-propionyl chloride (16-2) dissolved in a small amount of absolute ether was added to 0.8 Moles of freshly prepared diazomethane in ether, prepared according to the procedure in 2.A. Gas evolution was observed, the reaction flask

allowed to stand overnight mounted with a CaCl_2 tube and filtered the next day to remove any polymeric material formed. The ether was evaporated and to the dark oil benzene was added to azeotrope out any water on the mixture. It was assumed that 0.02 Moles (100% yield) of the diazoketone were obtained in order to determine what amount of $\text{BF}_3(\text{Et})_2\text{O}$ ought to be used in the next step.

At a later time fractions 16-1 and 19-1 of the acid chloride were combined (5.63 grams or 0.028 Moles), dissolved in ether, and added to 0.12 Moles of freshly prepared diazomethane. The diazoketone was treated as before and it was assumed again that a 100% yield had been obtained in order to determine the quantity of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ needed.

5. Preparation of 5-phenyl-tetrahydrofuranone-3'

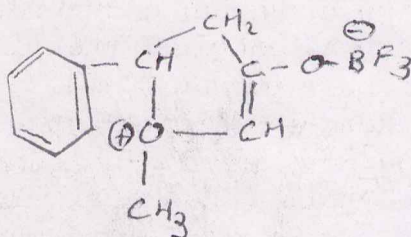
Approximately 0.02 Moles of 1-diazo-4-methoxy-4-phenyl-butanone-2 in 10 ml. of ether was added slowly to 4.32 g (0.03 Moles) of Boron trifluoride etherate dissolved in 100 ml. of ether. The reaction was carried out in a 250 ml. round bottom flask which was attached

through a trap to an inverted graduated cylinder for collecting nitrogen. The reaction seemed to begin immediately on addition of diazoketone as the solution began turning a darker and darker red and a rapid evolution of nitrogen was observed. As addition of diazoketone continued, the rate of gas evolution decreased, probably because of the decreasing concentration of reagents. The solution was neither heated nor stirred, although it is now thought that stirring would have been advantageous. The reaction was discontinued in about an hour when 375 ml. of nitrogen gas had been collected and the mixture was very dark. Using the ideal gas law, this corresponds to a diazoketone yield, in the first part of step 4 of 83.5%. The solution was filtered into a large separatory funnel (separating the tars) and extracted twice with water, once with NaHCO_3 , and once again with water, saving the ether layers each time. The ether layer was filtered through anhydrous sodium sulfate and evaporated on the aspirator. (Benzene was added to azeotrope off the water.) Evaporation of the ether yielded a sweet smelling red-orange solid as the crude reaction

product (17-1). 17-1 melted from 50° - 55° C. and an infra-red spectra showed the presence of a carbonyl group (5.8 - 5.9μ); ether group (8.5 - 9.3μ); and non-substituted benzene group (see Figure 4A). Some of 17-1 was recrystallized from ether and gave light yellow crystals melting at 95° C. (18-2). The remaining crude product was recrystallized from ether and low boiling ligroin to give impure gold-colored crystals melting at about 80° C. (18-3). The mother liquor was recrystallized to give gold-colored crystals of substantial purity, melting at 92° C. (SJ1-1). An IR of SJ1-1 gave a cleaner-looking version of the IR of 17-1. SJ1-1 indicated 66.29% carbon and 5.11% hydrogen. For 5-phenyl-tetrahydrofuranone-3, the calculated percentages are carbon - ~~24.04%~~ and hydrogen - 6.22%. Some of the aforementioned by-products give calculated percentages closer to the experimental values. The ether-ligroin mother liquor was allowed to stand for several weeks until the solvent had evaporated and a whitish (barely yellow) solid melting at 109° C. remained (18-4). The IR taken (Figure 4B) is quite similar to 4A but is evidently purer as the peaks are sharper and more well defined. This is peculiar that the mother liquor should yield a pure product. The crude product weight was inadvertently not taken

although the yield is estimated at 40-50%. A DNP derivative of 18-4 yielded a deep maroon solid with a melting point of 104-105°. This derivative will be recrystallized and sent out for carbon-hydrogen analysis.

At a later date, approximately 0.028 Moles of diazoketone in ether were added to 0.042 Moles (ratio of 1.5 to 1) of $\text{BF}_3 \cdot (\text{Et})_2\text{O}$ in ether and 300 ml. nitrogen collected over the course of the reaction. By the ideal gas law this volume represents only a poor 47.9% diazoketone yield on the previous step (the diazoketone formed from 16-1 and 19-1). The reaction conditions were exactly the same as those previous. Because it is thought that the reaction intermediate



is stable and thus possible to isolate, before the addition of water at the end of the reaction, an infra-red spectra of the reaction mixture was taken (see Figure 4C). The result is very much like Figures 4A and B and it is difficult to say with certainty whether or not this spectra shows proof of the existence of the intermediate. Bands at 6.85-7.12 μ

and 7.41-7.63 μ represent B-CH₃ and B-O linkages respectively and although this spectrum contains peaks at both these wavelengths, so do Figures 4A and 4B which are not intermediates, so no positive judgment can be made. The solution was then extracted and evaporated and the crude product was a dark colored viscous liquid (20-1) weighing 2.29 grams (0.007 Moles) representing a 25% yield, calculated as cyclic product.

The IR of 20-1 (see Figure 4D) is similar to those previous. Vapor phase analysis of this product (Figure 4E) showed one major peak (75%) and four minor peaks. This in itself is a good indication that the ring compound (the most likely) was formed. The DNP derivative of product 20-2 had a melting point of about 85°. Preparation of more of this DNP for recrystallization and analysis is still going on. A small sample of crude product was recrystallized from ether to yield a few light beige crystals melting at 125°C. and apparently very pure (20-2). The IR of a too dilute sample, much like those before, is shown in Figure 4F. Using an F and M Model 720, VPC with a preparatory column 20-1 was fractionated and the substance expelled from the column over the area of the large peak (see Figure 4E) was collected.

The pure fraction is an almost colorless crystalline solid (it is thought). Enough will now be collected for an NMR analysis (0.2 grams).

SUMMARY AND CONCLUSION

The synthesis has been completed and there remains only the analysis of the products. There is good reason (though by no means positive proof) to believe that the compound, a major product, probably 5-phenyl-tetrahydrofuran-3 has been formed. If the mechanism postulated in the Introduction is correct, the ring structure is the most probable product and the single major peak on VPC analysis, leads one to be hopeful. The infra-reds of the various final crude and crystallized products show positive evidence of the ketone, ether, and monosubstituted benzene group, but are by no means sufficient evidence to enable one to substantiate the five-membered ring. That on the first BF_3 run the crude product was a solid and in the second, an oily liquid, need not lead one to believe that two different products may have been formed, in each case. In the first BF_3 reaction, water was added upon completion of the reaction; in the second, water was not added until several hours after completion. In both cases I think the main product is the ring compound, but in each case, because

of the slightly different reaction conditions, different proportions of by-products may have been formed. In the first case there may have been less such impurities, hence, the crude product was a solid, while in the second case increased amounts of impurities may have depressed the melting point so much that the crude product was a liquid at room temperature. Further analysis proposed in the last section should establish the results of this investigation.

The successful preparation of α -methoxyphenyl-acetyl chloride was the breakthrough in the synthesis. An IR run on this acid chloride the day after its preparation showed by peak analysis about 80% acid chloride and 20% benzaldehyde. After three weeks of refrigeration of the acid chloride, IR showed about 40% acid chloride and 60% benzaldehyde, indicating the instability of α -methoxyphenyl-acetyl chloride and also suggesting that it seems possible to carry out kinetic studies of this decomposition to determine its mechanism. This acid chloride decomposes rapidly and therefore must be reacted with diazomethane within one or two days of its preparation. Belli (3), although he got low yields in the Arndt-Eistert synthesis because of not having successfully prepared the acid chloride, suggested that the

lengthening of the carboxylic acid chain by one CH_2 unit accomplished through a diazoketone intermediate, would be a satisfactory method in the synthesis. The work done this year has proved Belli correct. For future work, it is strongly recommended that the procedures set forth through the preparation of β -methoxy- β -phenyl-propionic acid be followed closely. A large amount of α -methoxy-phenyl acetic acid should be used to start as the synthesis yields from start to finish is low (about 7.5%). It would be helpful indeed to have this acid as pure as possible and if there are pure and impure fractions, they ought to be kept separate and reacted separately to insure high purity in at least some of the end products. A classical method for the preparation of α -methoxy phenyl propionyl chloride ought to be used (e.g. Wagner and Zook). The BF_3 reaction procedure should be experimented with. Perhaps an excess of BF_3 should be used or more should be added when the reaction slows down. Also suggested is experimenting with Boron Trifluoride isopropyl etherate. The purpose of this would be to prevent the formation of the etheroxy open chain compound by steric hindrance.

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FIGURE 1A

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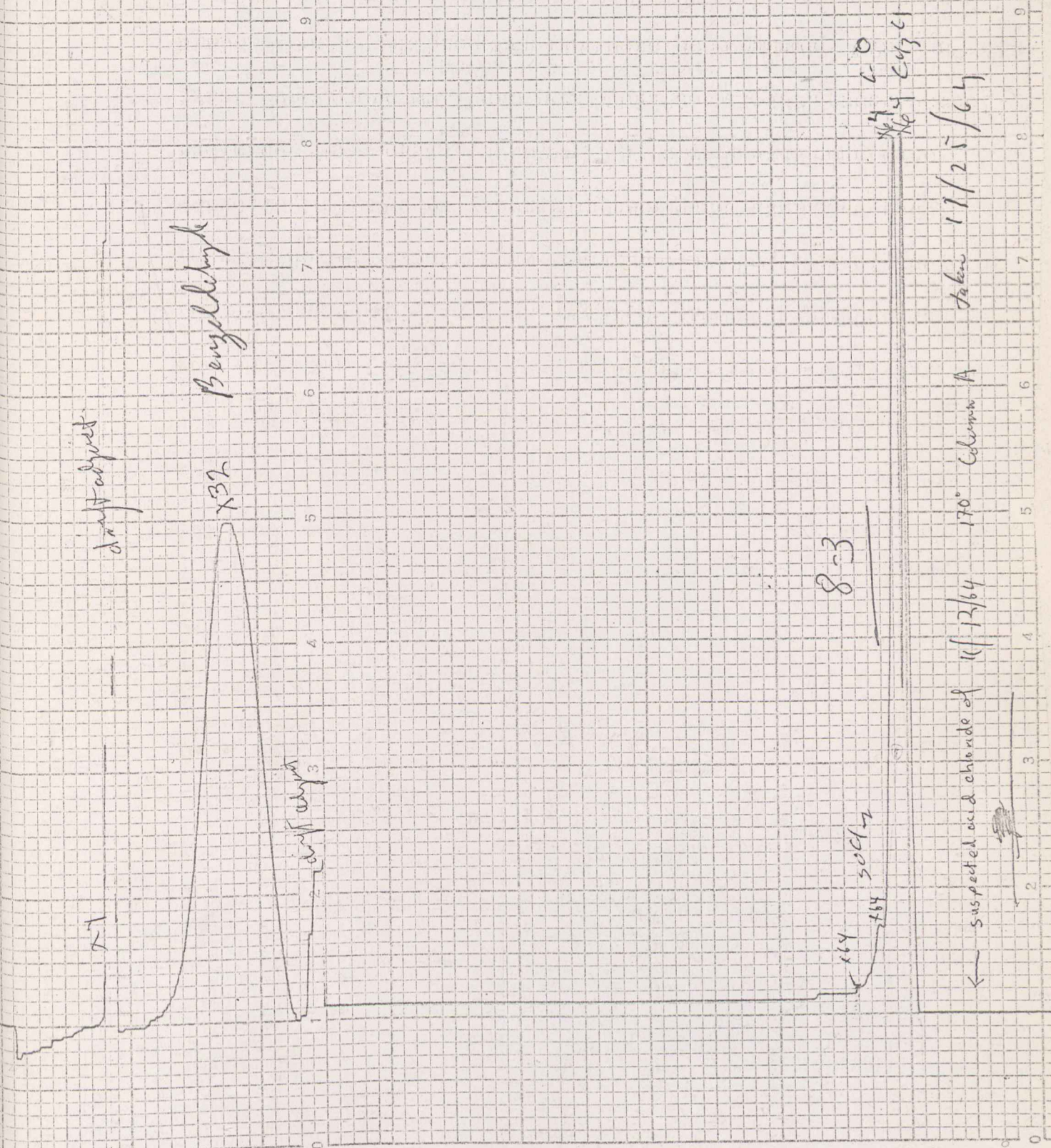
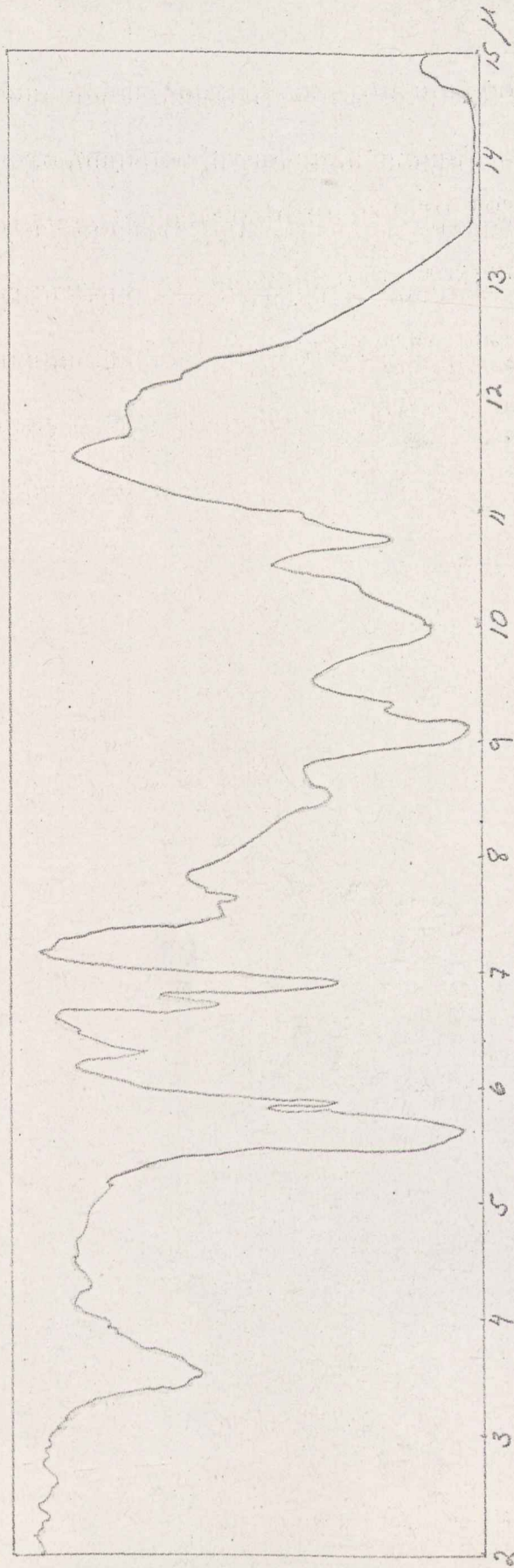


FIGURE 18



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FIGURE 2

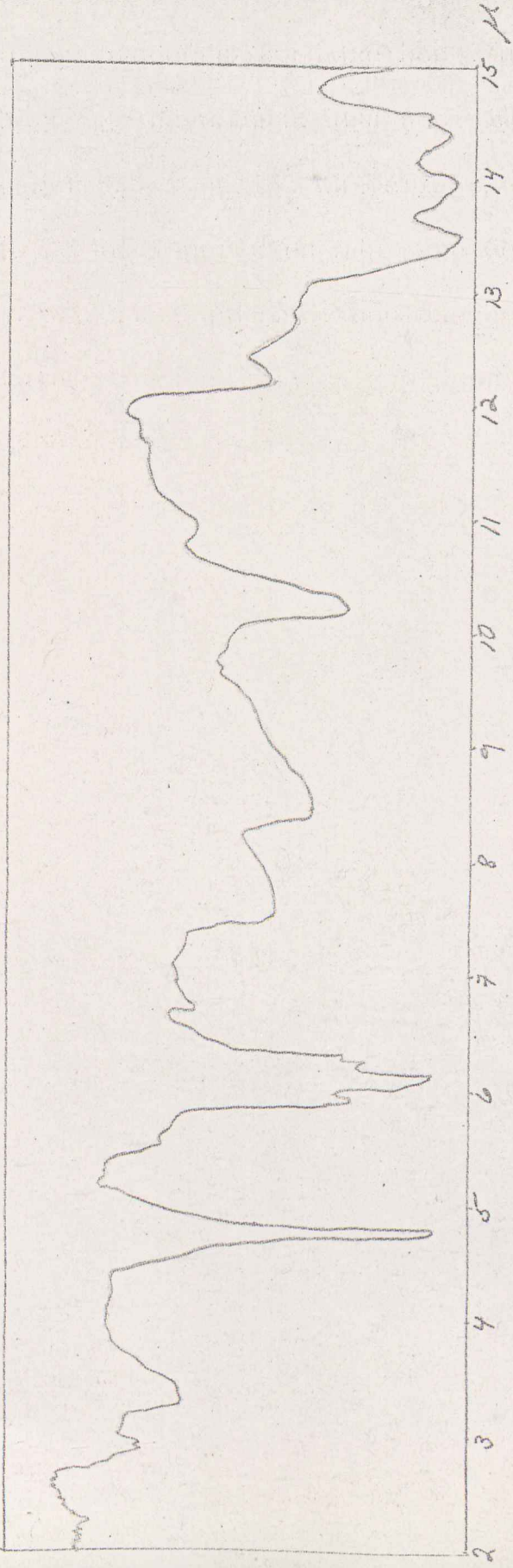


FIGURE 3

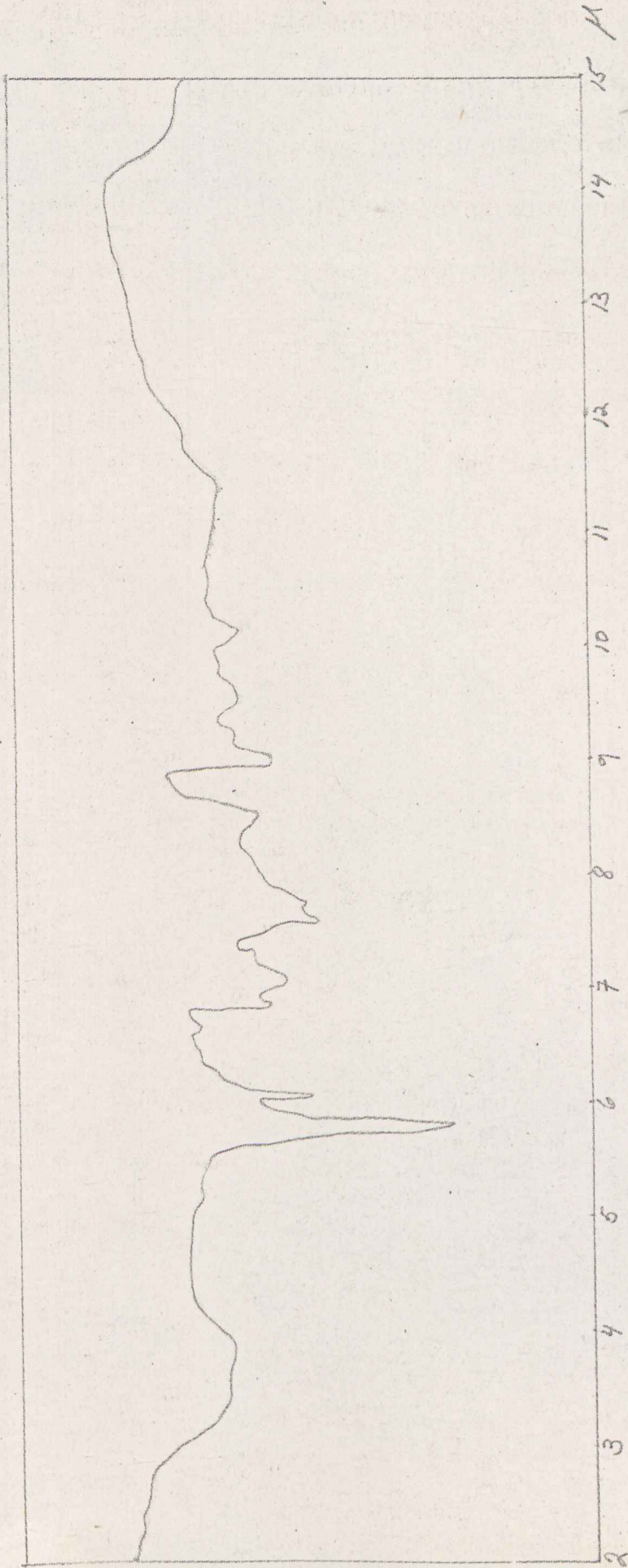
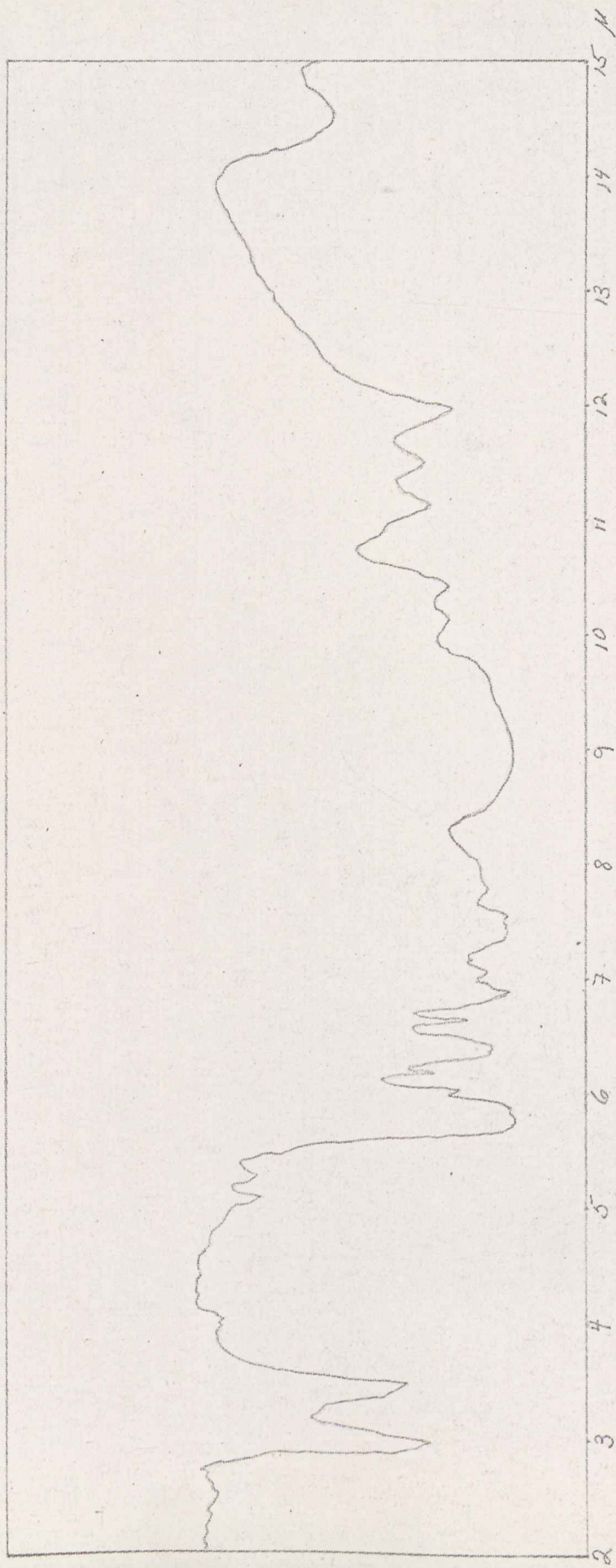


FIGURE 4A



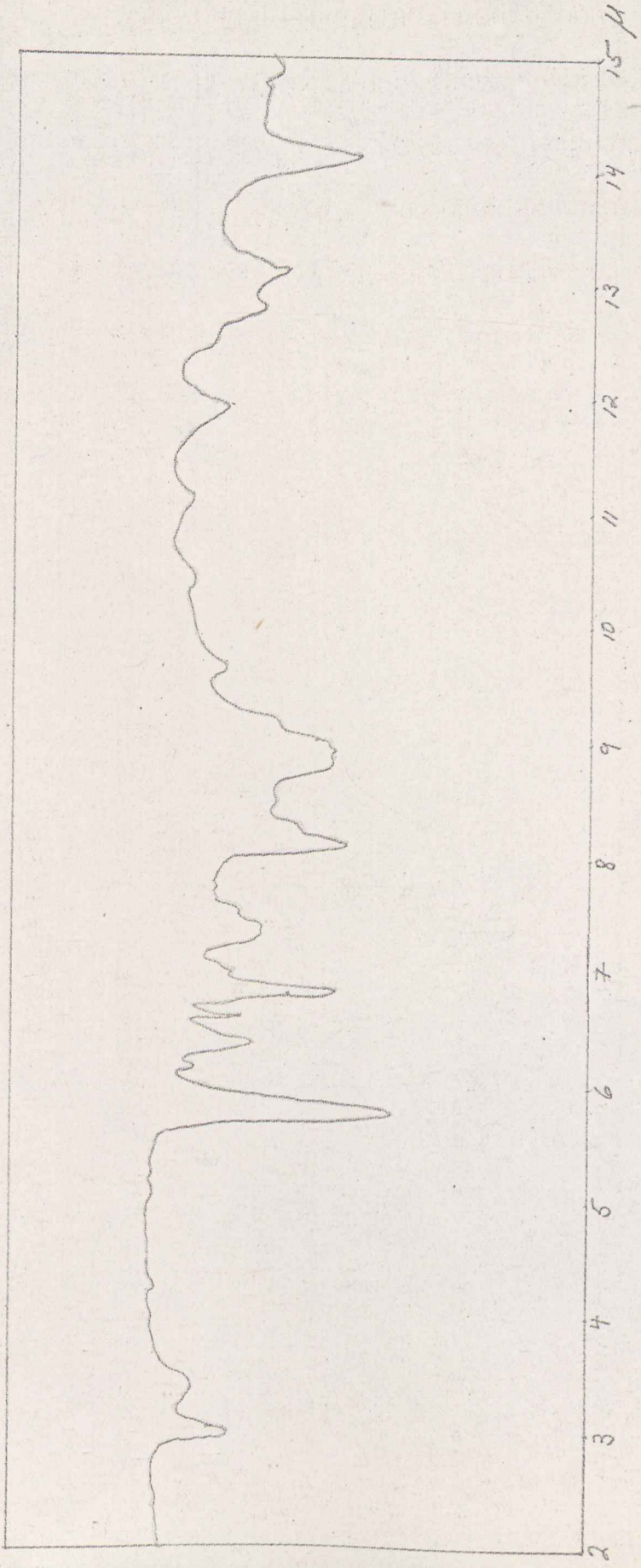


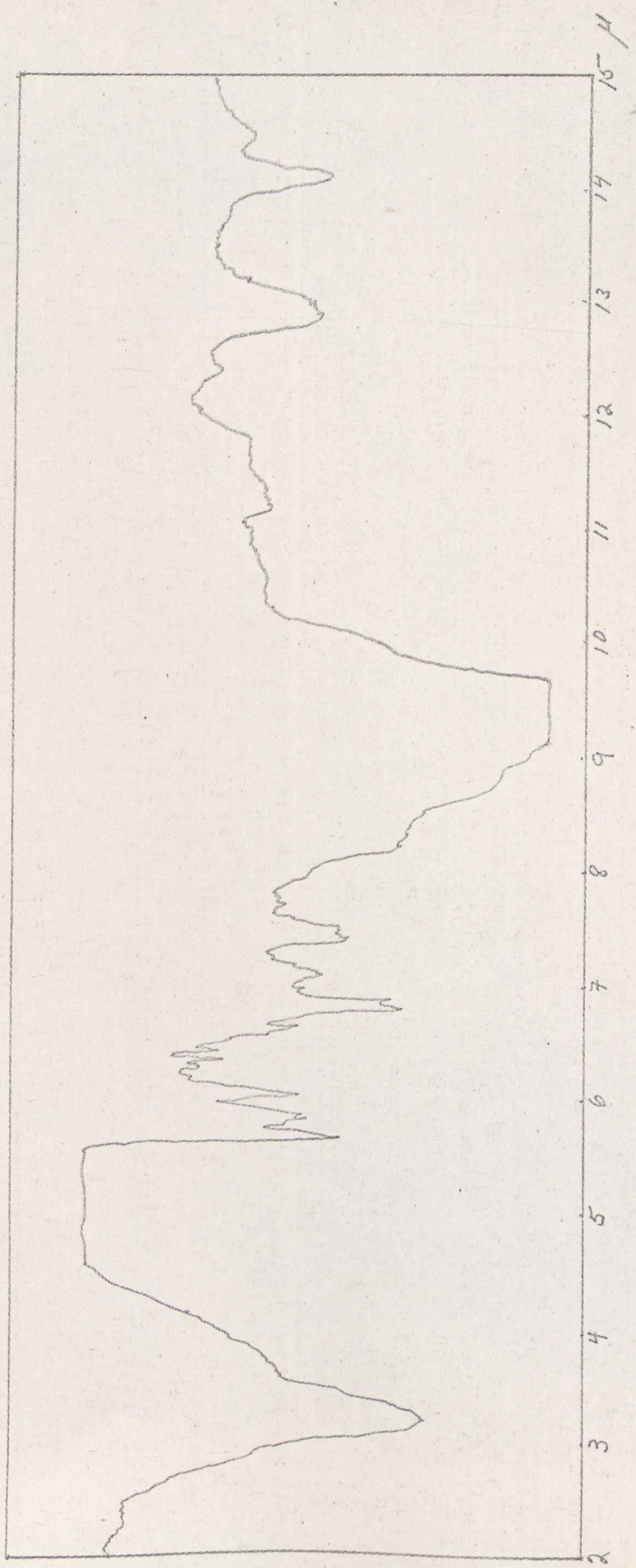
Figure 4B

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Figure 4c



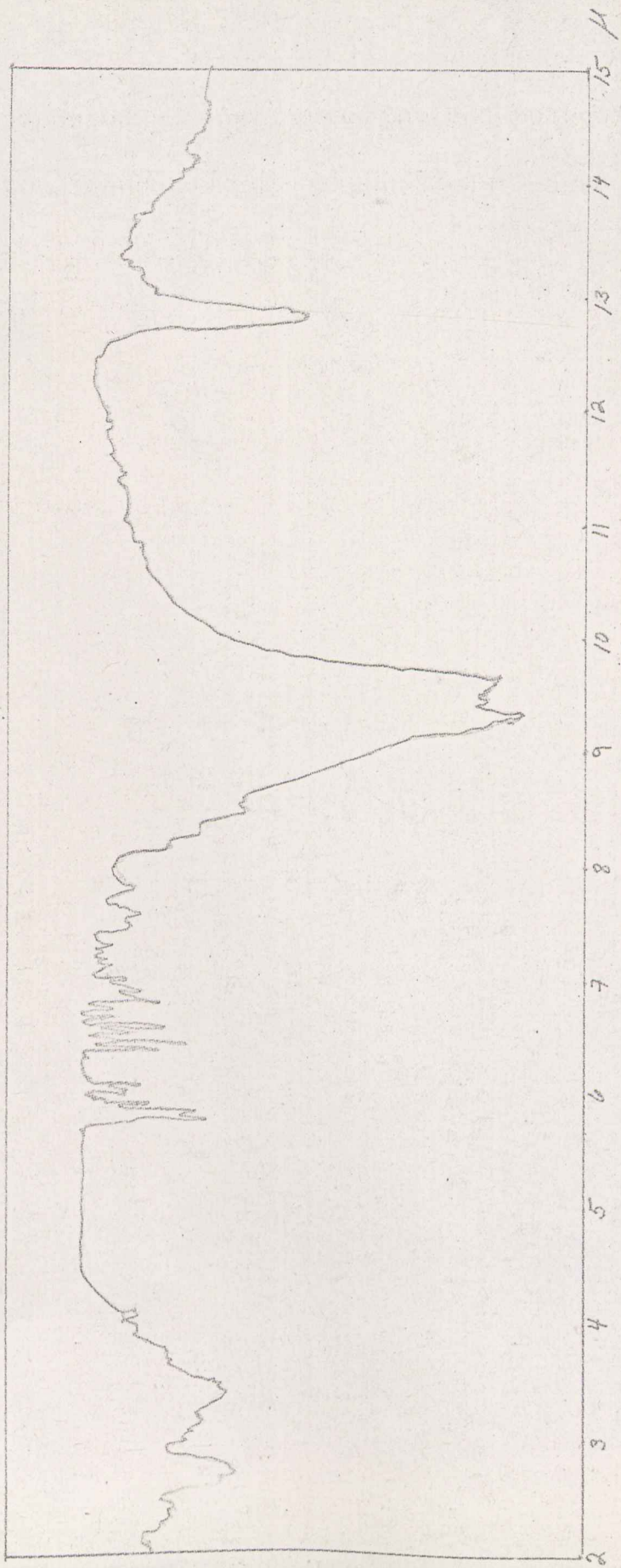


FIGURE 4D

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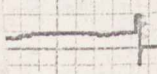
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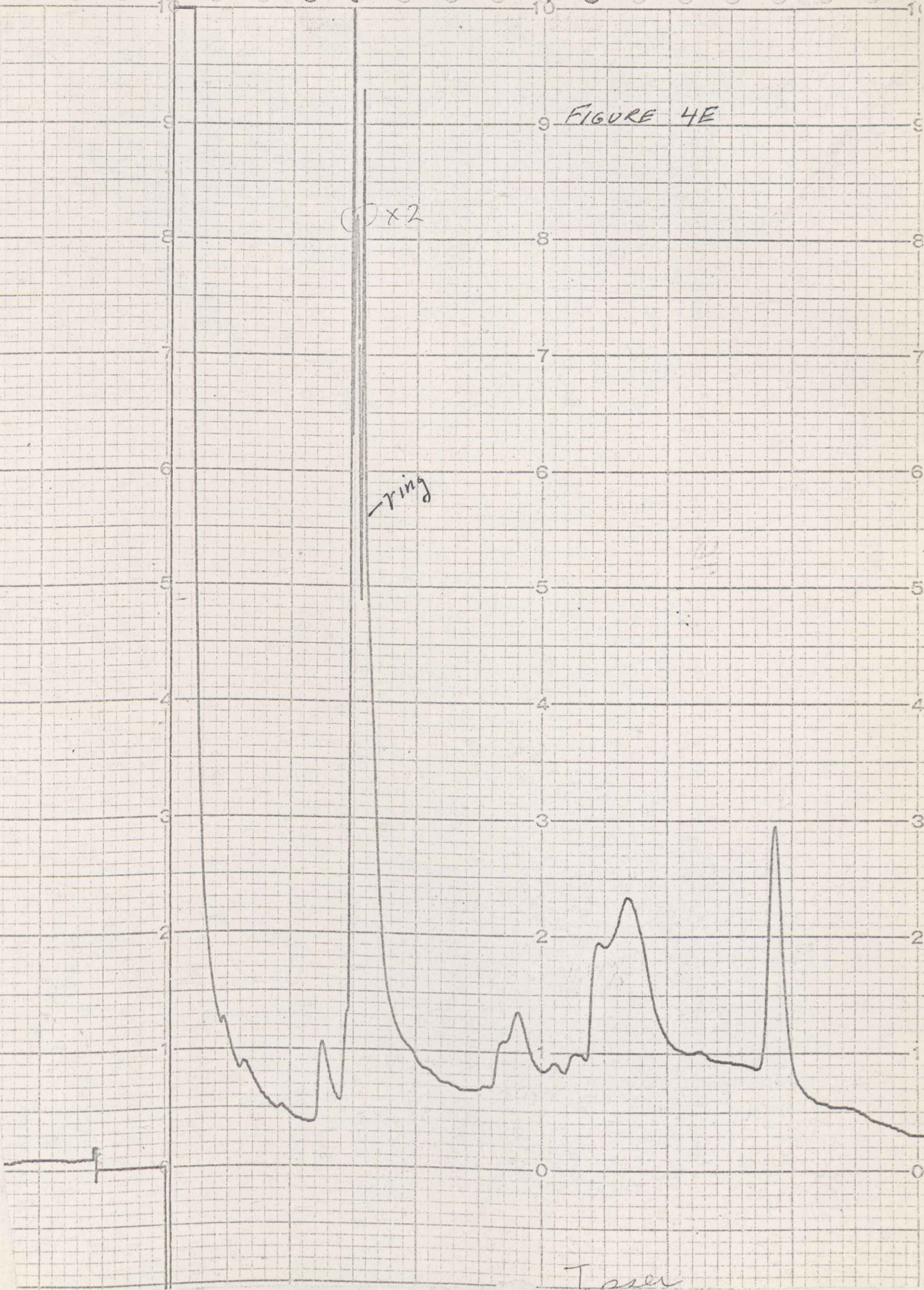
FIGURE 4E

(D) x 2

ring



Taser



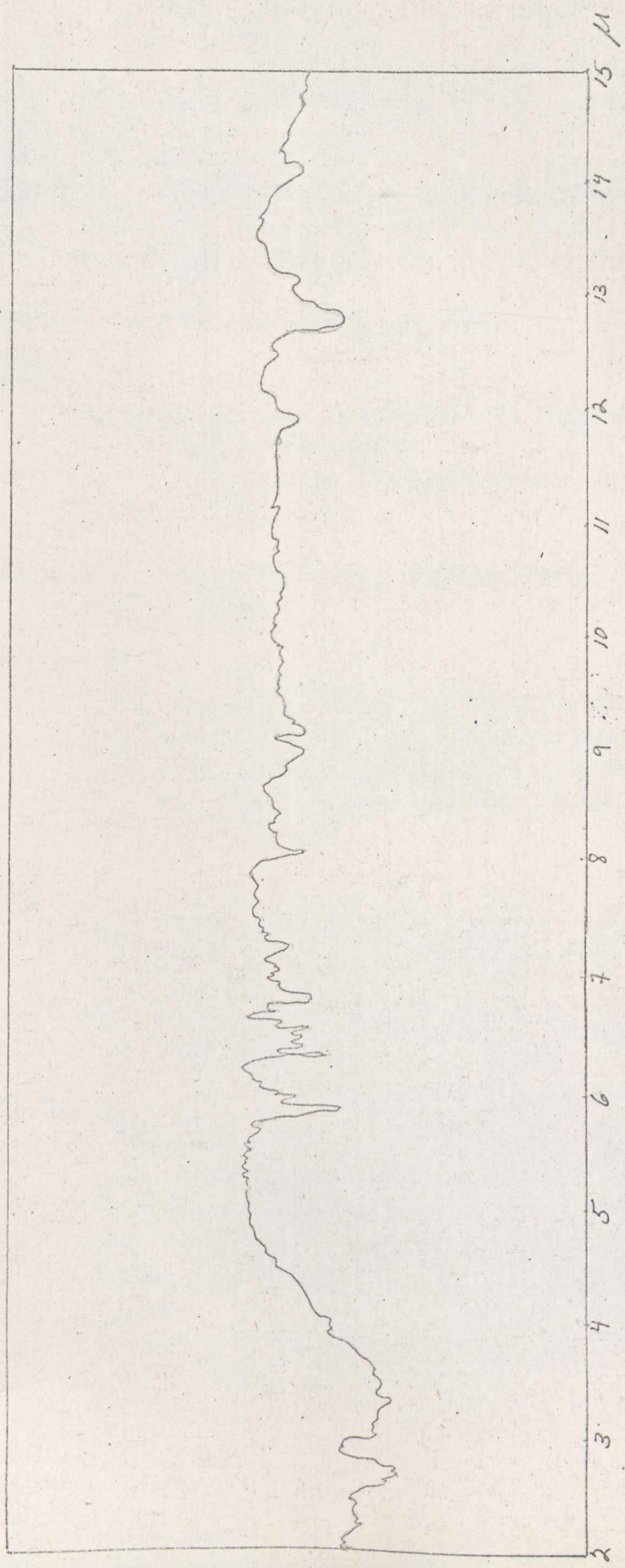


FIGURE 4F

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