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ASPECTS OF THE REACTIONS OF
ALIPHATIC METHOXYDIAZOKETONES

by

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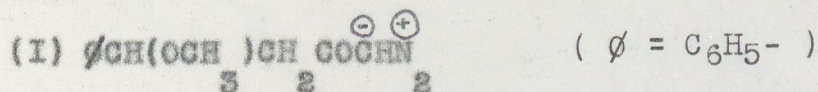
I would like to express my gratitude to Dr. H.E. Sheffer, professor of Organic Chemistry at Union College, for his assistance. I would like also to thank H.H. Kagan for his help.

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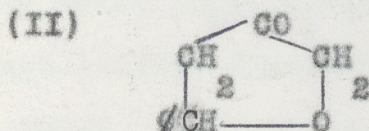
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INTRODUCTION

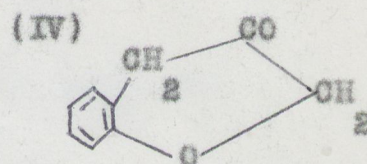
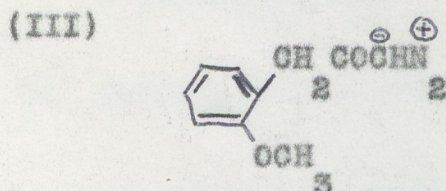
It was the purpose of this research to investigate the cyclization of the aliphatic methoxydiazoketone, 1-diazo-4-methoxy-4-phenyl-2-butanone (I), when treated with BF_3 in ether



to give the five-membered ring 5-phenyltetrahydrofuranone-3' (II)



Cyclic products from diazoketones have been obtained in the aromatic series with systems having ortho-substituents using BF_3 . An example may be found in J. Moore and H. Sheffer(12) in which 1-diazo-3-(o-anisyl)-2-propanone (III) yields chromanone (IV) when treated with BF_3 (yield 35%)



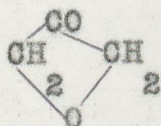
From the above example it appears that cyclization is favored by the Lewis acid BF_3 , because when mineral acids were used a lower yield of chromanone was obtained.

Four-membered rings are possible to form in aliphatic systems only from α -methoxy ethers because of the nature of aromatic systems. Attempts to synthesize four-, and five-membered rings in aliphatic systems have been made during the 1962-63 academic year by W.H. Thielking (13) and D.P. Hoster (7). The syntheses

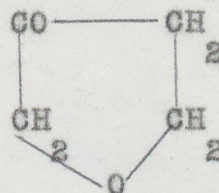
were not completely successful, although evidences of fluoro-ketones and 1-hydroxy-3-methoxy-2-propanone were obtained.

Hoster (7) tried to produce the cyclic compounds oxetanone-3 (V) and tetrahydro-3-furanone (VI)

(V)

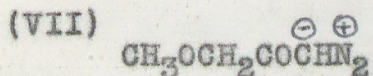


(VI)

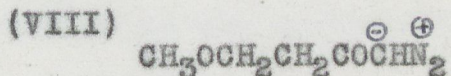


by using $\text{BF}_3 \cdot (\text{C}_2\text{H}_5)_2\text{O}$ on 1-diazo-3-methoxy-2-propanone (VII) and 1-diazo-4-methoxy-2-butanone (VIII) respectively.

(VII)



(VIII)



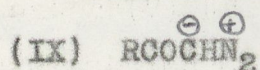
Based on these considerations, the proposed route to the synthesis of (II) starting from d, l-mandelic acid can be schematically given as follows:

- 1) $\phi\text{CH}(\text{OH})\text{COOH} \xrightarrow{\text{NaOH aq}} \phi\text{CH}(\text{ONa})\text{COONa} \xrightarrow{(\text{CH}_3)_2\text{SO}_4} \phi\text{CH}(\text{OCH}_3)\text{COONa} + \phi\text{CH}(\text{OCH}_3)\text{COOH}$
- 2) $\phi\text{CH}(\text{OCH}_3)\text{COONa} \cdot \phi\text{CH}(\text{OCH}_3)\text{COOH} \xrightarrow[\text{reflux}]{\text{SOCl}_2} \phi\text{CH}(\text{OCH}_3)\text{COCl}$
- 3) $\phi\text{CH}(\text{OCH}_3)\text{COCl} \xrightarrow{\text{CH}_2\text{N}_2^{\ominus\oplus}} \phi\text{CH}(\text{OCH}_3)\text{COCHN}_2^{\ominus\oplus} \xrightarrow[\text{H}_2\text{O}]{\text{Ag}} \phi\text{CH}(\text{OCH}_3)\text{CH}_2\text{COOH}$
- 4) $\phi\text{CH}(\text{OCH}_3)\text{CH}_2\text{COOH} \xrightarrow[\text{reflux}]{\text{SOCl}_2} \phi\text{CH}(\text{OCH}_3)\text{CH}_2\text{COCl} \xrightarrow{\text{CH}_2\text{N}_2^{\ominus\oplus}} \phi\text{CH}(\text{OCH}_3)\text{CH}_2\text{COCHN}_2^{\ominus\oplus} \xrightarrow[\text{ether}]{\text{BF}_3} \text{(II)}$

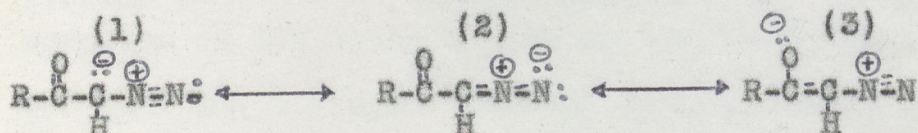
The outlined syntheses will be discussed in the experimental section.

HISTORICAL

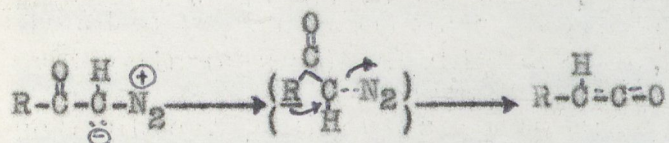
Diazoketones have the general formula (IX)



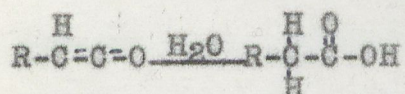
in which R is any alkyl or aryl group. The actual structure of (IX) is a resonance hybrid of the following forms:



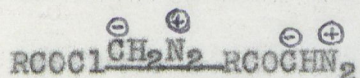
Diazoketones were discovered by the German chemist L. Wolff (15) at the beginning of the twentieth century. The Wolff rearrangement of diazoketones, formally similar to the Curtius rearrangement, has probably the following mechanism:



The ketene formed yields the acid RCH_2COOH upon addition of water:



The method of preparation of diazoketones in good yield (80%) is due to F. Arndt and B. Eistert (1). After subsequent modifications, the method is known as the modern preparation of diazoketones. An acid chloride $RCOCl$ is converted to the corresponding diazoketone upon treatment with diazomethane in a cold ($0-5^\circ C$), ethereal solution.



The acid chloride can readily be obtained from the homologous carboxylic acid in a yield up to 70% or better. The conversion to the diazoketone and the subsequent formation of the

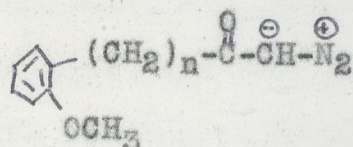
carboxylic acid with longer chain RCH_2COOH provide an easy way of lengthening the carbon chain.

The preparation of a carboxylic acid from the diazoketone is known as the Arndt-Eistert synthesis. Although the mechanism of such a reaction is not clear, it is proposed that it may proceed by a free-radical mechanism (8). It is a fact that the reaction is catalyzed by silver compounds (usually silver oxide), but possibly a copper compound such as cupric oxide catalyzes the reaction more effectively. Cupric oxide has been successful in the preparation of carboxylic acid esters from diazoketones and alcohols, although the formation of an ether group may occur(4).

Diazoketones are usually reacted as soon as they are prepared, because they are unstable even at room temperature and decompose with evolution of nitrogen. They may be stored, using great care, for a period of one-two weeks at $0-5^\circ\text{C}$. A variety of products are obtained when the diazoketones decompose in acid solutions, the substituted methyl ketones being predominately observed. But instability and preparation of higher homologous carboxylic acids, esters, amides are not the only features of diazoketones. The cyclization reaction is a property that has been studied in the aromatic and only recently started in the aliphatic series of diazoketones. Only a few works done in the aromatic series are dealt with here. For a more extensive treatise the reader should consult Hoster (7). In general it is observed that cyclic products are obtained from favorable ortho-substituted diazoketones of acetophenone. Bose and Yates(3)

report the formation of coumaranone upon treatment of 2-diazo-o-methoxyacetophenone with mineral acid. Coumaranone is also produced by treating α -diazo-o-acetylacetophenone with glacial acetic acid as reported by Elderfield and co-workers (5).

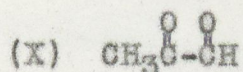
When mineral acids are used there is nucleophilicity competition between the anion of the mineral acid and the methoxy-oxygen. To overcome this situation and increase the nucleophilicity of the methoxy-oxygen to bring about ring closure, the use of a Lewis acid such as BF_3 as been suggested by Sheffer and Moore(12). They found that the system



undergoes cyclization best when n is equal to zero or one and a Lewis rather than a mineral acid is used.

The work done in the aliphatic series is less encouraging. Marshall and Walker (6) reported the preparation of oxetanone-3 (V) starting with chloro-acetic acid. Hoster (7) obtained fifteen fractions, still impure, when 1-diazo-3-methoxy-2-propanone was reacted with BF_3 in ether. Infrared analysis-Perkin-Elmer Model-21 infrared recording spectrophotometer with NaCl cells-gave evidence of $-\text{OH}$, ROR , $\text{C}=\text{O}$, CF groups. One of the above fractions that showed only two peaks in the V.P.C. analysis-Perkin-Elmer Model 154-D vaporfractometer with "R" column-was separated into two parts by condensation of the effluent vapor in a dry-ice-acetone bath. One of the two fractions gave 2,4-dinitrophenylhydrazone derivatives with a

melting point of 300°C corresponding to bis-2,4-dinitro-phenylhydrazone of pyruvaldehyde (X)



Four-fractions not analyzed were obtained when 1-diazo-4-methoxy-2-butanone (VIII) was treated with BF_3 in ether. In Hoster own words ".... the synthesis of oxetanone-3 and tetrahydro-furanone-3 by the reaction of the corresponding methoxydiazoketones with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was unsuccessful". Evidences of open-chain hydroxyketone (1-hydroxy-3-methoxy-2-propanone) and fluoroketone, but not for ethoxyketone were given.

The present research is a consequence of the principles outlined above, aiming to bring more light in the reactions of diazoketone in the aliphatic series. It is based on the work done in the aromatic diazoketones, trying to extend the same mechanistic theory. The title reflects the idea that the work in this area has only begun.

APPARATUS

Common laboratory glassware apparatus were used throughout the experimental work. Only glass-joints apparatus were used.

The Perkin-Elmer Model 21 Infrared recording spectrophotometer with NaCl cells, and the Perkin-Elmer Model 154-D vapor-fractometer equipped with an "R" column were used for analysis. The vapor-fractometer was used to check the purity of fractions, while the infrared spectrophotometer to determine the functional groups present in reactions products.

EXPERIMENTAL

1) Preparation of α -methoxy-phenyl acetic acid:

α -Methoxy-phenyl acetic acid was prepared by the method described by W.R. Reeve and I. Christoffel(10).

In a 5-gallon glass-can (in order to minimize the effect of foaming during methylation) 707.0 grams of NaOH previously dissolved in 2.3 L of boiling distilled water were placed and immediately 203.0 grams of d,l-Mandelic acid were added. The resulting solution had a light-brown color. The solution was stirred in order to dissolve quickly the acid. When all the acid was in solution the bath temperature was cooled down to 50.0°C by using an ice bath. From a 2000-ml separatory funnel (rinsed with acetone and dried) 700.0ml of di-Methyl sulfate-not redistilled before using it-were added to the reaction bath very slowly. At the beginning of the reaction fumes were observed. After 45 minutes of constant addition of Methyl sulfate the temperature in the reaction bath was 55.0°C and it was necessary to cool it down to 50.0°C by using an ice-water bath. After one hour the speed of addition of dimethyl sulfate was increased. Where the dimethyl sulfate came in contact with the reaction mixture, fumes were constantly given off. The temperature was continuously raising and care was taken to maintain it at 50.0°C. The reaction ended in a period of one hour and 45 minutes. The reaction mixture was allowed to stand in the covered glass-can for 48 hours

to make sure that all the gases formed and the unreacted di-methyl sulfate were gone, the latter being poisonous. The reaction was carried out in a well ventilated hood because of the toxicity of di-methyl sulfate. The reaction mixture was filtered under reduced pressure and the precipitate (A)-brownish crystals-put in the oven at 50°C for 24 hours to dry. A filtrate aliquot, tested for sulfate ions, gave a positive test with lead acetate. Addition of technical NaCl to the filtrate allowed the recovery of more product. This was treated as precipitate (A) and the two were combined giving a total of 210.9 grams dry weight. The obtained product was soluble in water in the ratio of 1.0 gram per 3.0 ml and insoluble in ether. To the obtained product dissolved in 830.0 ml of hot (80°C) distilled water 22.0 ml of concentrated hydrochloric acid were added slowly and in portions giving a resulting pH in the range of 2-3. The resulting mixture was allowed to cool down at 20°C and then filtered under reduced pressure. The followings were obtained:

a) A clear filtrate to which 70 grams of technical NaOH were added allowing the recovery of 2.0 more grams of the final product.

b) A white precipitate of 141.0 grams.

The combined 143.0 grams of the final product were redissolved in 1410.0 ml of boiling distilled water, cooled down at 20°C in an ice bath, and the filtered precipitate dried in the oven

@ 50°C for 24 hours gave a 81.3 grams of dry weight (yield 39.2%). The product was analyzed by titration with standard aqueous 0.1187 N NaOH using three drops of phenophthalein as indicator and the results are summarized in table 1-A.

Table 1-A

Sample No.	1	2	3
Weight of sample in grams	0.0701	0.0958	0.1700
Volume in ml of NaOH	1.55	2.35	4.30
N.E.	381	340	333

N.E. average: 351

Calculated N.E. for the acid: 166

Calculated N.E. for the acid and its Sodium salt: 354

The N.E. found (351) checks with the calculated N.E. for the acid and its Sodium salt (354). The reported N.E. (10) is 354.3.

d,l-Mandelic acid gives upon treatment with aqueous NaOH with subsequent addition of dimethyl sulfate α -methoxy-phenylacetic acid. The reactions are given in 1, page 2. While one would expect to obtain only the methoxy acid, the above value for the neutralization equivalent suggests that a mixture of the acid and its Sodium salt in a ratio of 1:1 is obtained.

In order to obtain the acid, the acid-sodium salt mixture could be dissolved in hot distilled water adding enough concentrated hydrochloric acid to make the pH of the solution acidic. The acid then could be extracted with ether from the acidic solution. This procedure however was not used, because the work done by Santhwick and Seivard (11) showed that it is possible to prepare an acid chloride from the salt of the acid. Santhwick used 1 mole of $(KO)OC-CO(OCH_3)$ and 1 mole of $SOCl_2$, the acid chloride being obtained by distillation from the cake of potassium chloride.

2) Preparation of α -methoxyphenylacetyl chloride:

α -Methoxyphenylacetyl chloride was prepared by the method suggested by Santhwick and Seivard (11).

The mixture of the acid and its sodium salt was placed in the oven @ 60°C for 24 hours to dry. In a 500-ml 3-necked flask mounted with condenser and a separatory funnel 34.50 grams of the acid-sodium salt mixture were placed and 15.0 ml of thionyl chloride were added slowly in a period of 25 minutes (0.6 ml/min.) through the separatory funnel. Heat was supplied by a heating mantel for the first ten minutes. After $\frac{1}{2}$ hour a light-brown cake was obtained and heat was again supplied continuing the reflux for three more hours. At the end of the reaction the supernatant liquid was poured in a 50-ml distilling flask and the remaining solid rinsed twice with 10-cc portions of thionyl chloride, the washings being added in the distilling flask. The distillation was carried out at atmospheric pressure (758 mmHg) and only the fraction boiling in the 175-185°C range was collected. The distillate was redistilled under the same conditions as above giving a fraction boiling in the range 178-180°C, this being the B.P. of α -methoxyphenylacetyl chloride as ascertained in subsequent as well as concurrent work. The separatory funnel was used to obtain a constant addition of thionyl chloride. In order to prevent introduction of water vapor from the surrounding atmosphere a calcium chloride tube was mounted on the condenser.

The results obtained in the preparation of α -methoxyphenyl-acetyl chloride are summarized in table 2-A

Table 2-A

Compound	grams used	Mol. weight	grams expected	grams obtained	% yield	B.P. C 758mmHg
Acid and Sodium salt	34.50	$\frac{166.2}{188.0}$	-	-	-	-
Thionyl chloride	40.20	118.9	-	-	-	-
Acid chloride	-	184.5	35.06	7.50	21.39	178-180

3) Preparation of β -Methoxy- β -phenyl-propionic acid;

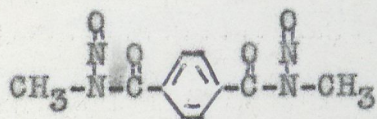
A) Preparation of diazomethane:

Diazomethane was prepared according to the procedure described by Reed and Moore (9).

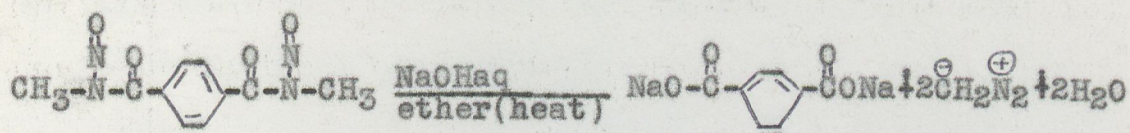
In a 1-L round, 3-necked flask 600 ml of ether, 90 ml of diethylene glycol-monoethylether (Matheson, Coleman and Bell), and 120 ml of 30% aqueous NaOH solution were placed.

The mixture was chilled in an ice-sodium chloride bath to 0°C and finally 36 grams (0.1 mole) of bis-(N-methyl-N-Nitroso)terephthalimide (XI) (E.I. Dupont Co.)

(XI)



were added in portions. The flask was immediately transferred to a heating mantle and connected by a goose neck to a 60-cm condenser connected to a receiving flask. The pressure built inside the receiving flask during distillation was controlled by using a stopcock. Enough absolute ether was placed in the receiving flask to cover the tip of the adapter in order to minimize loss of diazomethane. The yellow color of diazomethane appeared in the receiver almost immediately and about 0.5 L of ether-diazomethane were distilled in one hour. The reaction ends when the yellow color is no longer present in the distilling flask according to the reaction:



The entire reaction was carried out in a ventilated hood and great care was used in handling the toxic diazomethane. A theoretical yield of 0.2 moles of diazomethane was to be obtained from the used amount, while the actual yield was about 0.16 moles since a 80% yield is to be expected (7). 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:

1-methoxyphenylacetyl chloride (0.045 moles) diluted with ten ml of absolute ether were added to the freshly prepared diazomethane in ether of A. Gas evolution was observed after about five minutes, lasting for ten minutes. The reaction mixture was then left overnight in the hood to make sure that all the diazomethane was gone. The flask was stoppered with a one hole-rubberstopper mounted with a calcium chloride tube. After one day the reaction mixture was filtered to get rid of the formed polymeric material and finally the ether was evaporated under reduced pressure. No heat was applied in order not to decompose the diazoketone, although a warm-water bath would have speeded up the process of evaporation. It took six hours to completely evaporate the ether. Seven grams of 1-diazo-3-methoxy-3-phenyl-2-propanone were obtained (yield 80%).

C) Preparation of β -methoxy- β -phenylpropionic acid:

(The Arndt-Eister synthesis)

The β -methoxy- β -phenyl propionic acid preparation was attempted according to the methods described in (1) and (14). Silver oxide (Ag_2O) (1.00grams) -previously prepared by adding 10% NaOH solution to 100 ml of 10% AgNO_3 solution avoiding excess of the former, washing ten times with distilled water, filtering by suction, and again washing with water the brown precipitate-, anhydrous sodium carbonate (2.50 grams), sodium thiosulfate (1.50grams), and distilled water (100.0 cc) were placed in a 2000-ml round 3-necked flask. Seven grams of 1-diazo-3-methoxy-3-phenyl-2-propanone in 70.0 ml of p-dioxane were delivered to the reaction mixture by using a separatory funnel in order to regulate the flow of the diazoketone at constant rate of addition. A mechanical stirrer was used to provide constant and thorough mixing and a heating mantel to supply heat to the reaction mixture. The nitrogen evolved was collected in water in a graduated cylinder, a trap being used between the reaction flask and the cylinder to avoid the water from going into the flask.

The Apparatus assembly is shown in figure 1, page 17.

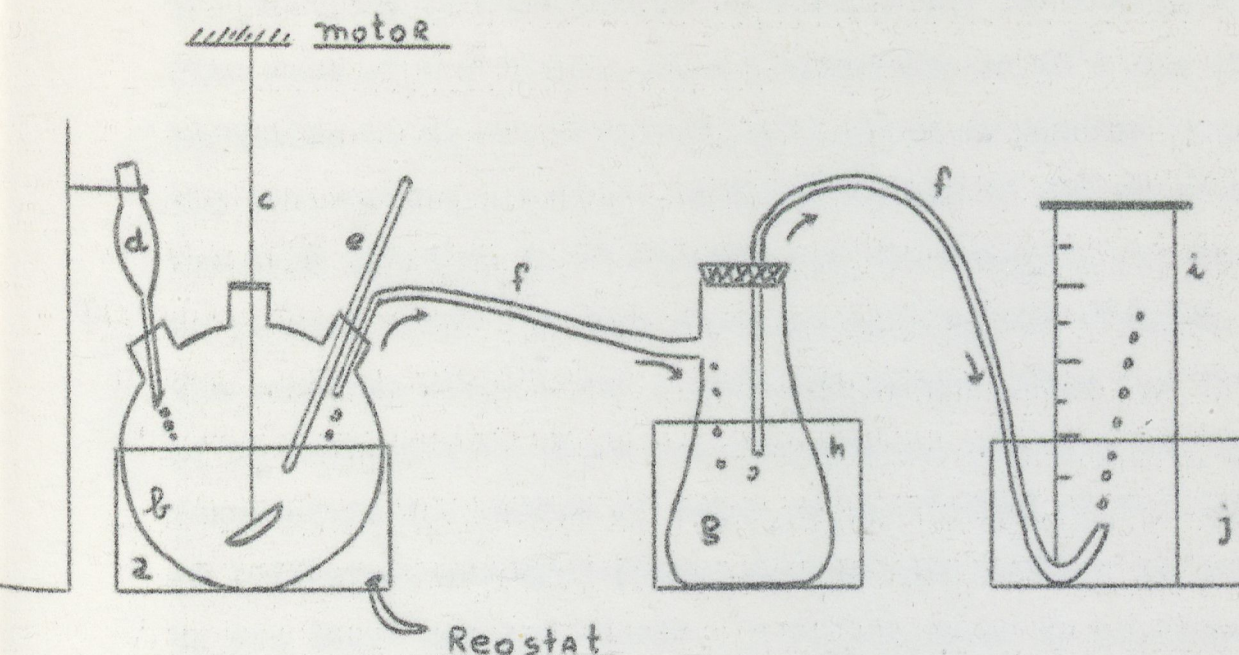


Figure 1

a-Heating mantle

b-Reaction flask

c-Mechanical stirrer

d-125-ml Separatory funnel

e-Thermometer

f-Glass and rubber tubes

g-Trap

h-Ice bath in order to cool any vapor that might escape from the reaction flask

i-Graduate cylinder to measure the N_2 evolved

j-Water bath as receiver of the water from the graduate cylinder

The addition of diazoketone in dioxane was started at a constant flow rate of 2.8 ml/min. at a temperature of 25°C and no evolution of N_2 was observed until after 45 minutes when the temperature was 52°C. A total volume of 200 ml of N_2 was then obtained in 15 minutes and the reaction was thought to be over after 1- $\frac{1}{2}$ hour since no more N_2 was evolved. The reaction mixture had a greenish color. From the volume of N_2 collected at about one atmospheric pressure and 25°C temperature the number of moles of N_2 evolved or the number of 1-diazo-3-methoxy-3-phenyl-2-propanone reacted is computed by the ideal gas law $PV=nRT$. A 0.0084 moles is so found, indicating to a first approximation a 23.3% yield. The reaction mixture was filtered out and the solution extracted five times with small portions of ether. These extracts were discarded. The clear aqueous solution was carefully acidified with dilute HCl (1cc concentrated HCl to 2cc water), 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 four 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 Na_2SO_3). The sodium hydroxide extracts were yellow. The united NaOH extracts were acidified with dilute HCl, saturated with technical NaCl, and extracted with ether as before. The ether is evaporated on a hot plate and a crude product of

0.6535 grams melting at 90°C was obtained. The yield was 10% calculated on the basis of the number of moles of α -methoxy-phenylacetyl chloride (0.036 moles). The M.P. of β -methoxy- β -phenyl-propionic acid reported in the literature (2) is 98°C. A prepared 10% solution of the product in ether (0.172 grams acid in 2.0cc ether) was analyzed for purity on the Perkin-Elmer Model 154-D vaporfractometer and two relatively small peaks were associated with a major one. The neutralization equivalent analysis (titration with aqueous NaOH) showed a 85% purity.

In a second attempt to prepare more β -methoxy- β -phenyl-propionic acid, α -methoxy- α -phenylacetic acid (Eastman Organic Chemicals) was chosen as starting material. The procedure outlined on pages 14 through 19 was followed. These remarks and changes however are to be noted:

- 1) In the distillation of the acid chloride at atmospheric pressure (759mmHg) two fractions were obtained:
 - a) Colorless fraction B.P. range 178-183°C
91.95 grams (0.494 moles) were obtained (yield 41.4%)
 - b) Yellowish fraction B.P. range 183-196°C
11.73 grams were obtained

2) In the preparation of diazomethane five times as much as the amount indicated on page 14 was used. The reaction lasted 2- $\frac{1}{2}$ hours.

3) As the acid chloride was added to diazomethane gas evolution was observed immediately. The diazoketone was kept for a week in the refrigerator without decomposition.

4) The following amounts of reagents needed for the Arndt-Eistert reaction were used:

Ag₂O: 5 grams
 anhydrous Na₂CO₃: 12 grams
 Na₂SO₃: 7 grams
 distilled water: 500 ml
 diazoketone in 300cc of dioxane (the diazoketone was assumed to be about 0.3 moles based on previous yield)

5) Instead of adding the diazoketone at 25°C the reaction mixture was preheated at 60°C and N₂ was evolved immediately upon addition of diazoketone (50ml/min. flow rate). A total of 1200ml of N₂ were collected giving 0.052 moles of N₂ (yield 18.6%). The acid yield was 8.2%.

4) Preparation of β -methoxy- β -phenylpropionyl chloride:

The procedure used for the preparation of β -methoxy- β -phenyl propionyl chloride is outlined on page 12. To 1.3701 grams of β -methoxy- β -phenyl propionic acid in a 5-ml flask mounted with small condenser, 1.00 ml of thionyl chloride was added. The reaction started immediately and was reflux for one hour. A 25% excess of thionyl chloride was added in order to assure complete reaction. The reaction product was distilled at 16mmHg pressure and two fractions were obtained:

Fraction 4-1: B.P. range 85-87°C at 16mmHg (about 1cc)

Fraction 4-2: B.P. range 120-170°C at 16mmHg (about $\frac{1}{2}$ cc)

This reaction was run for purity more than on a quantitative purpose analysis. The fraction 4-1, almost colorless boiling at 85-87°C as compared with α -methoxy- α -phenyl-

-acetyl chloride that boils at 75°C at the same pressure, is the desired product. V.P.C. analysis showed 90% purity with one major peak. Addition of alcoholic silver nitrate solution to an aliquot of the acid chloride gave an immediate precipitate, indication of reactive halogen. 0.3957 grams of the acid chloride were obtained giving a yield of 26.7%. The work done has confirmed the attempted route to lengthen the carbon chain of one-CH₂- unit through a diazoketone intermediate to be satisfactory at least for the purpose for which the route given was sought in the first place. The low yield obtained in the Arndt-Eistert synthesis however made the reaction interesting in itself. When the obtained 8-10% yield is compared to the claimed 70-80% in the literature (1) some considerations about the reaction were necessary. It was then decided to devote the remaining time to a general review of the Arndt-Eistert synthesis.

5) A review of the Arndt-Eistert synthesis:

1-diazo-3-methoxy-3-phenyl-2-propanone (0.46 moles) in 600 ml of 1,4-dioxane were added in a period of 15 minutes to a 3000-ml 3-necked flask containing 1200cc distilled water, 30.0 grams anhydrous sodium carbonate, 18.0 grams sodium thiosulfate powder, and 12.0 grams silver oxide (Ag_2O) freshly prepared, preheated at 50°C . (Fig.1 page 17). A rapid evolution of N_2 was observed immediately and 0.79 L N_2 were collected. Other 0.13 L were evolved in 45 minutes, the bath temperature remaining constant at 50°C . At higher temperature (90°C) 3.63 L of N_2 were collected in a three hours period giving a total yield of 38%. The reaction product was filtered, the filtrate acidified with dilute HNO_3 and extracted with five portions of 100-ml of ether. The ether was evaporated and the product passed through anhydrous sodium sulfate. A 48.05 grams of yellowish material-sample 5-1- was obtained. The V.P.C. analysis showed that the product obtained was quite impure. 1.1359 grams of 5-1 in 30.0 ml of 10% NaOH were extracted with two portions of 10-ml of ether. The first extract was yellow, while the second was clear. The ether layer -sample 5-2 - was passed through anhydrous sodium sulfate, the ether was evaporated and 0.1824 grams were obtained. The aqueous layer was acidified with 28.0 ml of 10% HCl , and extracted with three portions of 10-ml of ether. The aqueous layer was clear, while the ether layer was yellowish. The ether layer -sample 5-3- was passed through Na_2SO_4

anhydrous and the resulting crystals - M.P. 92°C- weighed 0.1684 grams. A 90% purity was shown by N.E. analysis by titration with aqueous NaOH. β -Methoxy- β -phenyl-propionic acid was recoverable in a 8.3% overall yield from the crude product. When 30.8045 grams of 5-1 were distilled at 20-25mmHg the following results were obtained:

Fraction No.	Sample No.	Boiling Point	Grams obtained
1	5-4	28-30°C	22.6436
2	—	30-50°C	—
3	—	50-90°C	—

The fraction No.1 was colorless, while the remaining were yellowish. The high-boiling material (over 210°C) was left in the distilling flask, dissolved in ether, extracted with two portions of 10% NaOH, acidified with 10% HCl, extracted twice with ether, and passed through anhydrous Na₂SO₄.

The resulting crystals melted at 93°C and gave a 8.0% yield, thus showing no improvement over the extraction method.

Fraction No.1 was found to be 98.4% pure by V.P.C. analysis. It afforded DNP derivative giving yellow crystals melting, after the third recrystallization, at 235°C..

The V.P.C. analyses for the samples No. 5-1, 5-2, and 5-4 are given in table 5-A on page 24.

V.P.C. analysis:

All V.P.C. analyses were obtained with the followings:

Perkin-Elmer Model 154-D vaporfractometer

"R" column

Temperature: 150°C

He pressure: 9 lbs/sq.inch

Voltage: 8 volts

Flow meter: 2.3

Power: 90

Sample volume: 10

Sensitivity: 2

Table 5-A

Sample No.	No. of peaks	Retention time in min. of peak No.					% of peak No.				
		1	2	3	4	5	1	2	3	4	5
5-1	5	1.4	2.2	5.8	8.0	41.8	0.3	0.2	0.4	93.1	6.0
5-2	3	1.4	-	-	8.4	39.8	0.1	-	-	37.5	62.4
5-4	3	-	-	5.0	7.8	41.0	-	0.1	0.1	98.4	1.5

SUMMARY AND CONCLUSION

Only a portion of the proposed project has been carried out experimentally. The acid needed in the attempted synthesis of 5-phenyltetrahydrofuranone-3 can be prepared from α -methoxy-phenylacetic acid, although in a moderate yield. The review of the Arndt-Eistert synthesis and the concurrent work done by Kagan (17) are of valuable importance in explaining the low yield obtained in the synthesis of β -methoxy- β -phenyl propionic acid. Kagan (17) obtained benzoic acid and acetophenone as the only identified products of treatment of α -methoxy-phenyl acetic acid with thionyl chloride followed by diazomethane and Boron trifluoride. Apparently the distillation of α -methoxy-phenyl-acetylchloride at atmospheric pressure leads to its partial decomposition into benzaldehyde (16). Using the volume of nitrogen evolved as evidence for the amount of undecomposed acid chloride, the yields of β -methoxy- β -phenylpropionic acid in runs 3-C (page 19), 3-C (page 20), and 5 (page 22) are 46.3%, 44.0%, and 20.6% instead of 10%, 8.2% and 8.3% respectively. Sample 5-4 was shown to be mostly p-dioxane by V.P.C., n.m.r., and I.R. analysis. p-Dioxane, used as solvent in the Arndt-Eistert synthesis, gave a peak of retention time 7.4 minutes when analyzed on the vaporfractometer under the same conditions as sample 5-4. The I.R. spectrum showed positively an ether

group. The proton n.m.r. spectrum (neat) showed a singlet at 6.45 τ and a very weak multiplet at 2.0 to 2.5 τ . The singlet corresponds to dioxane 6.30 τ (CCl₃). The multiplet indicates an aromatic compound. The DNP derivative of sample 5-4 was found to be the DNP derivative of benzaldehyde by mixed melting point and by comparison of the two I.R. spectra. Any attempt to prove the presence or absence of acetophenone was unsuccessful because the retention time of acetophenone almost coincides with that of p-dioxane. Unfortunately sample 5-2 was not saved. As future work, it is strongly suggested that α -methoxy-phenyl acetyl chloride be distilled under reduced pressure or used without distilling it from the reaction of α -methoxy-phenyl acetic acid with thionyl chloride.

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