6-1963

Synthesis and Reactions of Diazoketones

William H. Thielking
Union College - Schenectady, NY

SYNTHESIS AND REACTIONS OF DIAZOKETONES

by

William H. Thielking III

****

Senior Thesis Submitted
in Partial Fulfillment
of the Requirements for Graduation

DEPARTMENT OF CHEMISTRY

UNION COLLEGE

MAY, 1963

Synthesis and Reactions of Diazoketones

by

William H. Thielking

A thesis presented to the Departement of Chemistry of Union College in partial fulfillment of the requirements for the degree of Bachelor of Science with a Major in Chemistry.

By William H. Thielking

Approved by H E Sheffer

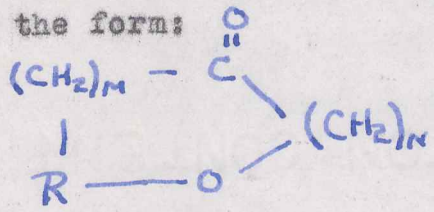
May 22, 1963

Acknowledgements

I would like to thank Professor Sheffer for his help, criticism and his encouragement during the course of this work. I would also like to extend my thanks to Donald Hoster and Robert English for their help.

Introduction

In recent years studies of diazoketones have been intensified because of their peculiar ability to under go cyclization under the proper acid conditions. The cyclic products have generally been of the form:

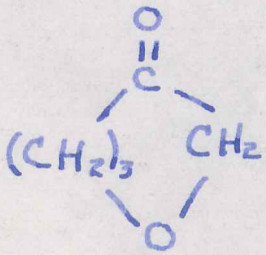


I

The cyclization itself is an interesting reaction and has come of some importance lately in the synthesis of drugs and hormones; especially those containing an aromatic ring(s) incorporated in a steroid system.

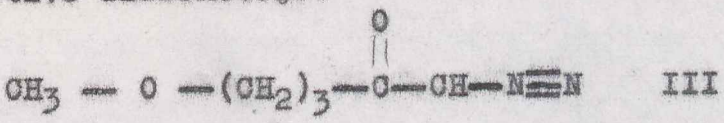
Heretofore studies of the cyclization have generally been confined to the synthesis of compounds similar to I where R is an aromatic ring and (m) and/or (n) have varied from 0 to 2, (1), (2), (4). At least one instance of the synthesis of a spiro compound is known, (3). These reactions have been reported as transpiring, with few exceptions, with better than 50% yields.

It is then the object of the present research, to extend the previous work to an aliphatic system by replacing the aromatic ring by one or more alkyl groups. Specifically, it is the object of this work to effect the closure of the ring compound;



II

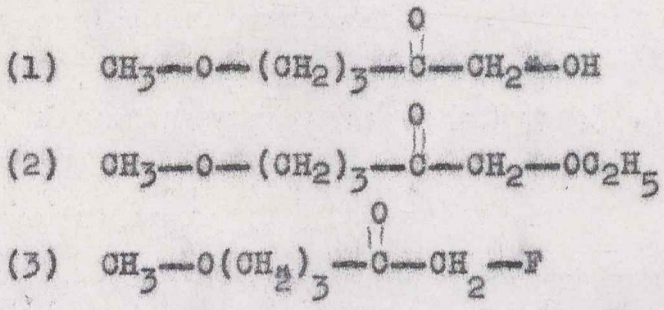
from its respective diazoketone:



III

The synthesis will proceed through the methoxyacid to III. Ring closure will be attempted by catalysis with BF_3.

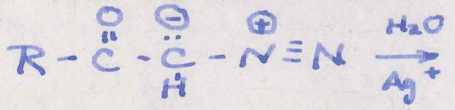
Because of the presence of more than one nucleophile in solution during ring closure there is the posibility of obtaining more than one product. Among the other products expected are:



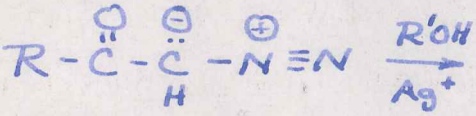
The direction in, annd the extent to which the reaction proceeds in a given direction, is then, a measure of the strength of the competing nucleophilies in solution.

History

Diazoketones were discovered at about the turn of the century by a german chemist, L. Wolff.[6] His synthesis is now considered laborious. Later studies by Wolff and his workers led to what is now known as the Wolff diazoketonesrearrangement[7] in which diazoketones rearrange to their corresponding acids or esters in the presence of silver ion.



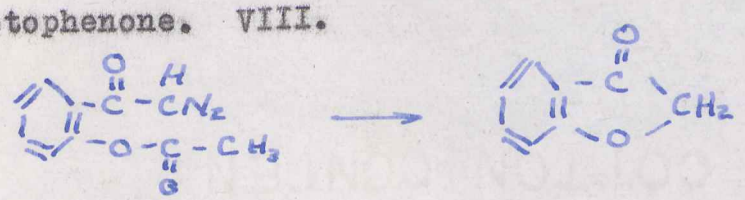
V



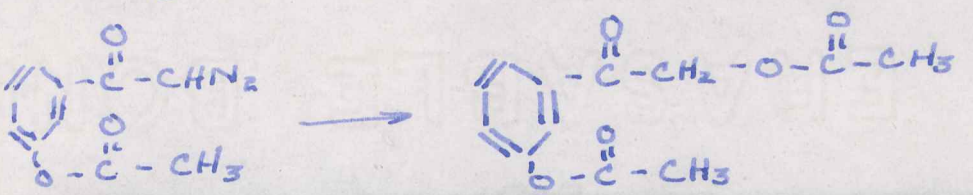
VI

In the late 1930's, Arndt and Eistert discovered the modern method of preperation of diazoketones;[8] that of converting the carboxylic acid chloride (or bromide) to the corresponding diazoketone by reaction with a cold ethereal solution of excess diazomethane. Further investigations of this proceedure today makes possible rapid preparation of diazoketones in better than 80% yields.

In 1942 Elderfield, Kuch and Marshall found that w-diazo-o-acetoxyl-acetophenone would generously yield coumaronone upon treatement with glacial acetic acid;[2] VII, while reaction of the corresponding meta compound, produced w-acetoxy-m-acetoxyl acetophenone. VIII.

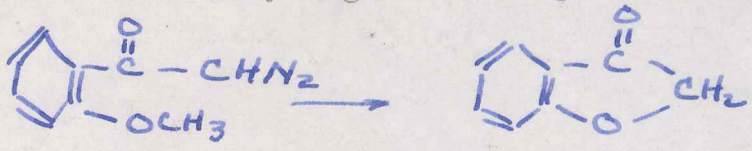


VII



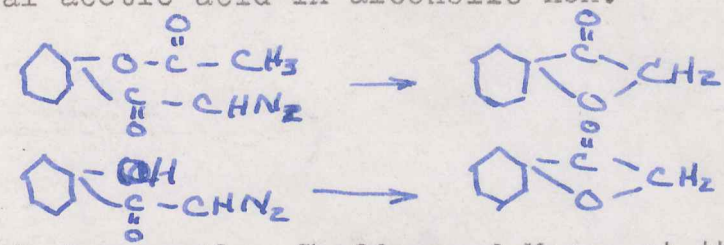
VIII

Ten years later Bose and Yates (1) observed the same effect when they treated diazo-o-methoxy acetophenone with a catalytic amount of hydrogen ion to produce coumaranone.



IX

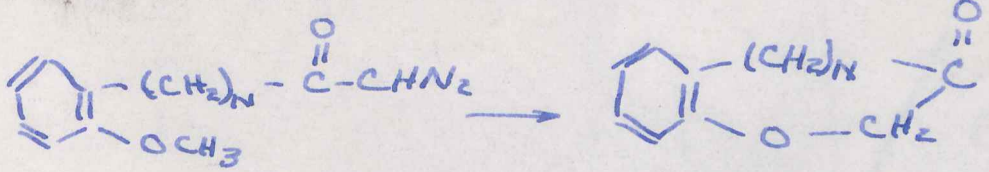
A similiar effect was observed by Herman who substituted an o-hydroxy group for the methoxide group. Marshall and Walker were able to affect closure of the spiro compound 1-oxaspiro-(3,5)-nonan-3-one by treating 1,1(acetoxy-w-diazoacetyl)cyclo-hexane X and 1-hydroxy-1-w-diazoaceto cyclohexane Xa with glacial acetic acid in alcoholic KOH.



X

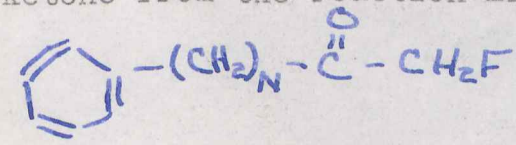
Xa

Most recently, Sheffer and More, at the University of Delaware, found that BF_3 would also catalyze ring closure as in V (4). They extended their work to include compounds having n equal to 1 or 2.



XI

It is interesting to note that they were also able to isolate a fluoroketone from the reaction mixture.

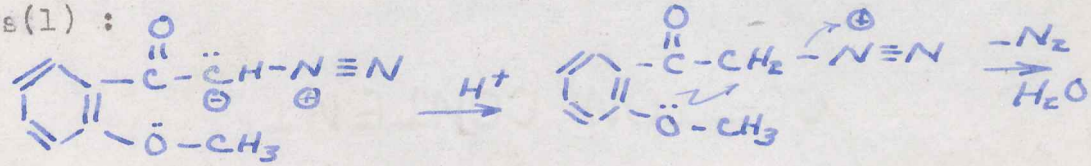


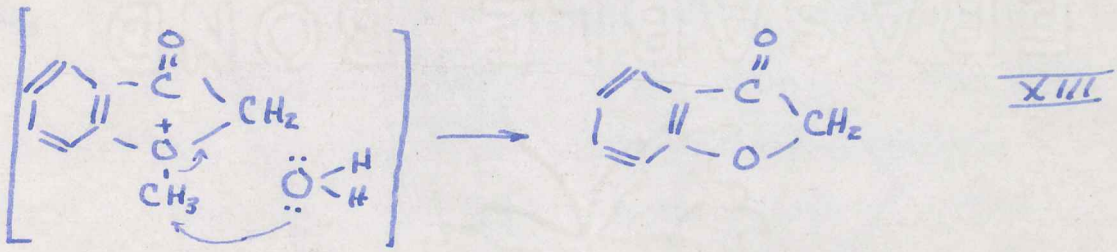
XII

The reaction mechanism of these cyclizations seems to be generally

understood as protination of the carbon adjacent to the diazo group, loss of nitrogen, nucleophyllic attack of a neighboring group and finally, hydrolysis of the resulting oxonium ion.

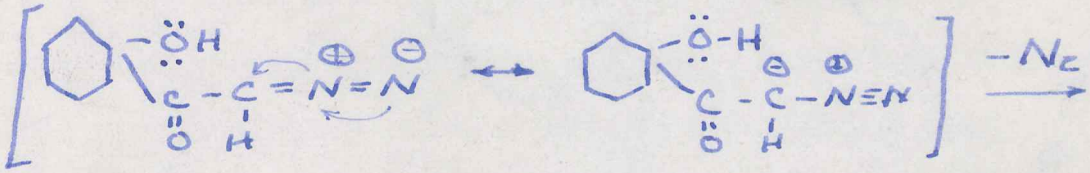
Elderfield and workers proposed the this mechanism as follows(1) :

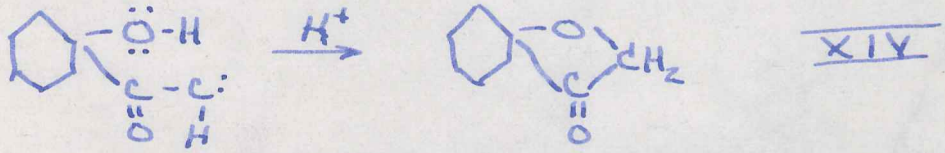




XIII

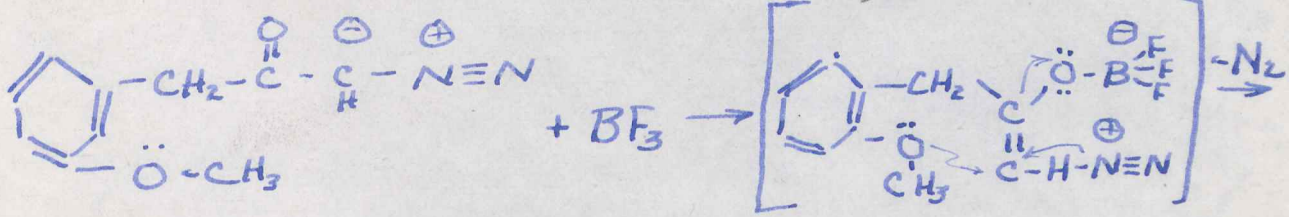
Marshall and Walker subsequently proposed the same mechamism for the formation of their spiro compound (3).

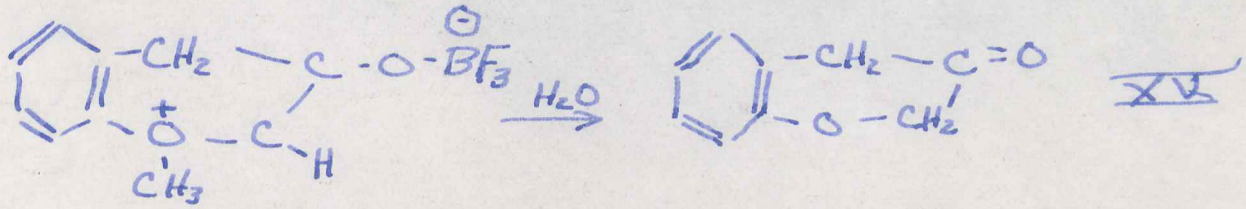




XIV

Most recently, Sheffer and Moore proposed an analogous mechanism for the closure of the ring using BF_3 as a catalyst.





XV

Experimental

Preparation of Sodium-γ- Hydroxy-Butyrate

(1) In a liter, three necked reaction flask with provisions for reflux, stirring and heating, 86 grams of γ-butyrolactone were placed. Sodium hydroxide in the amount of 40 grams and 150 milliliters of water were introduced. The mixture was stirred with refluxing for three hours. At the end of this time the resultant coffee colored solution was evaporated to dryness under heat and vacuum and the residue dissolved in 500 milliliters of boiling absolute ethanol. The product, recrystallized from ethanol, melted at 143-144 C. The reaction yielded 85 grams of sodium-γ-hydroxy-butyrate, (1-1) with a yield of 74 %.

(2) To 640 grams of γ -butyrolactone, proportionally larger amounts of sodium hydroxide and water were added as above. The reaction product was evaporated to dryness and dissolved in a liter of boiling absolute ethanol. The product, recrystallized from ethanol, was 720 grams of sodium-γ-hydroxy-butyrate, melting at 143 C, (1-2). Batches (1-1) and (1-2) were combined to give (1-3). The addition of alkali in the above proceedure should be undertaken slowly as the reaction is very exothermic.

Preparation of γ-Methoxy-Butyric Acid (5)

(1) To a three liter Gringard (three necked) reaction flask, with provisions for heating, stirring and reflux,

were added 125 grams of (1-3), sodium-γ-hrdroxy-butyrate. The entire apparatus was placed in a strong hood. To this were added 150 milliliters of 40% sodium hydroxide and the mixture was stirred untill complete solution was effected. Three 60 gram additions of dimethyl sulfate followed with 50 milliliters of 40% sodium hydroxide were spaced at one-half hour intervals. The mixture was stirred vigerously for one and one half hours at 50-60 C. The resulting milky solution was cooled to 25 C and neutralized to weak base, extracted with one fifty milliliter portion of ether and acidified further. The acid solution was extracted with ten - one hundred milliliter portions of ether. The ether from the first extraction contained unreacted dimethyl sulfate and was disgarded. The remaining extracts were combined and then evaporated. The residue was distilled to give 34 grams of crude product boiling from 213-233 C, (2-1) accompanied by a yield of 29%.

(2) A second batch of 250 grams of (1-3) were reacted as given above with correspondingly larger amounts of dimethyl sulfate and 40% sodium hydroxide. The ethereal extracts yielded 31 grams of product boiling from 220 to 230 C, (2-2).

Preparation of γ-Methoxy-Butyryl Chloride

(1) To 34 grams of (2-1), 35 grams of thionyl chloride were added in a well ventilated hood in a flask equipped with reflux condenser and heating mantle. The mixture was refluxed for one half hour and distilled to give a fraction boiling at 172-174 C. and weighing 23.5 grams(3-1). The reaction was accompanied by a 60% yield.

(2) Batch (2-2) was reacted in entirety, similiarly, with 35 grams of thionyl chloride. After a fifteen minute reflux period, the dark brown mixture was distilled to give four fractions.

Fraction #	Boiling Point	Weight
3-2 -- 1	20 - 120 C	4.20 grams
3-2 -- 2	120 - 172 C	5.10 "
3-2 -- 3	172 - 174 C	11.00 "
3-2 -- 4	174 - 200 C	1.19 "

Fractions (3-1) and (3-2 -- 3) were combined to give (3-5).

Preparation of Diazomethane

A five liter, three necked flask was equipped with a heating mantle, goose neck, and a long water condenser. The condenser was fitted with a long adapter provided with a stopcock (see fig. 1). The receiver was surrounded by an ice-salt bath capable of maintaining the five liter receiver at 0 C or lower. The ground glass joints were left ungreased.

The receiver was filled with enough annhydrous ether to cover the bottom of the adapter: about three hundred millliliters. In the reaction vessell were placed three liters of ether, 450 milliliters of 2(2-ethoxy, ethoxy)-ethanol, 600 millliliters of 30% sodium hydroxide and 180 grams of bis-(n,n' dimethyl, dinitroso,) terephthalamide (available from Dupont Company). The above were mmled to 9 C before admixture. The reaction mixture is heated until the reaction proceedes moderately, about 35 C, and the yellow diazomethane emherate starts to distill. Initially, the reactants turn a deep yellow. As the diazomethane distills, the slury like mixture looses its color and, at the termination of the process, is a light cream color. At this point or shortly before the heat is removed. When the distillate has lost the characteristic yellow color the stopcock is opened and the aparatus cautiously disengaged from the receiver which is subsequently provided with a rubber stopper and calcium chloride drying tube. The drying tube is an essential which protects the annhydrous diazomethane etherate from moisture. The etherate can be kept in the referigerator for from several hourssto a day. Light and heat tend to decompose the diazomethane.

Diazomethane is an unstable, extremely toxic gas. For these reasons it should be synthesized and handled in an efficient hood behind safety shields.

Preparation of 1-diazo-5- methoxy-2-pentanone

At room temperature the acid chloride (3-5) in 50 milliliters

of annhydrous ether was slowly added to the diazomethane etherate. The addition was accompanied by a slow, steady, evolution of gas. The gas was presumed to be methyl chloride. The ether was drawn off the golden reaction product at room temperature on a water aspirator to give (4-1). The product was stored in the referigator.

Borontrifluoride Reaction

One hundred milliliters of annhydrous ether were added to (4-1) , which was still in the five liter reciever at 9 C., and standing in the hood. Borontrifluoride (28 grams) etherate was dissolved in 450 milliliters of annhydrous ether and slowly added to the above to give (4-2). No noticeable gas evolution accompanied the reaction. The product (4-2) was filtered and washed with one hundred milliliters of water, one hundred milliliters of 30% sodium bicarbonate solution and finally one hundred milliliters of water. The ethereal solution was dried by filtration through annhydrous sodium sulfate and the etherate was evaporated at room temperature under reduced pressure on a water aspirator. The resulting solution was designated (7-1). Distillation of (7-1) at 12 mm. yielded several fractions:

Fraction #	Bath Temperature	Head Temperature	Volume
7-2	70 C.	30 C.	1 st. drop
7-3	85 C.	52 C.	.2 ml.
7-4	90 C.	64 C.	.2 ml.
7-5	89 C.	66 C.	.6 ml.
7-6	98 C.	68 C.	4.0 ml.
7-7	100 C.	69 C.	6.0 ml.
7-8	100 C.	68 C.	10.0 ml.

The infrared spectrum of (7-8) showed strong evidence of the presence of resonably pure γ-methoxy-butyric acid. The characteristic absorbtions of the expected products were not in evidence. For this reason another acid batch was synthesized to determine the purity and the nature of the products.

One hundred and fifty grams of the sodium salt (1-3) were reacted with dimethyl sulfate as before. The ether was stripped and the syrupy residue (6-0) fractionally distilled. (12 mm.)

Fraction #	Bath Temperature	Head Temperature	Volume
6-1	85 C.	34 C.	4.0 ml.
6-2	120 C.	50 C.	3.0 ml.
6-3	140 C.	99-107 C.	4.0 ml.
6-4	155 C.	128 C.	.5 ml.

Fraction (6-3) weighed 10 grams (7.0% crude yield). Its infrared showed the presence of strong alcoholic hydroxyl absorbtion. Two neutralization equivalence titrations showed the purity of methoxy acid to be 31.5% and 23.3% respectively. It was then concluded that the presently used method of synthesis (methoxylation) was inadequate because of the large amounts of γ-hydroxy-butyric acid contaminating

the reaction product and the small yields incurred. A new search of the literature was carried out and the following synthesis preformed.

Synthesis of γ-Methoxy-Butyric Acid (5)

To 600 milliliters of absolute methanol, 37 grams of metallic sodium were added in a three necked, three liter flask with stirrer, reflux condenser and heating provisions. To the above 141 grams of γ-butyrolactone were added and the batch was let stand 48 hours. At the end of this time it was refluxed at 75 C. for 24 hours, evaporated to dryness with heat under reduced pressure and redissolved in water upon the addition of 175 milliliters of concentrated hydrochloric acid. The resulting solution was extracted with ether. The extract was evaporated down to a thick syrup and redissolved in two hundred milliliters of water and forty milliliters of 40% sodium hydroxide solution. The resulting solution was extracted with ether and the ethereal solution disgarded. The aqueous layer was acidified and extracted with ether. The ethereal solution was stripped and fractionally distilled as given below. (15 mm. pressure)

Fraction #	Bath Temperature	Head Temoerature	Volume
	75 C.	30 C.	1 st. drop
11-1	100 C.	30-88 C.	5 ml.
11-2	134 C.	88-102 C.	5 ml.
11-3	150 C.	102-120 C.	20 ml.

Fraction (11-3) gave 17 grams of γ-methoxy-butyric acid having a neutralization equvalent of 137 (yield 8.7%) .

Preparation of γ-Methoxy-Butyric Acid

To 1200 milliliters of absolute methanol, proportionally larger (equimolar) amounts of metallic sodium and δ -butyrolactone were added. The reaction product was worked up as before to give a fraction boiling between 110 and 130 C. and weighing 33 grams (13-9). (8.5% yield) Sample (13-9) was combined with (11-3) to give (14-1). The neutralization equivalent of the mixture was 139. Batch (14-1) was distilled as below. (15 mm.)

Fraction #	Bath Temperature	Head Temperature	Volume
	123 C.	44 C.	1 st. drop
14-2	125 C.	44-90 C.	1.0 ml.
14-3	130 C.	90-91 C.	1.0 ml.
14-4	135 C.	91-130 C.	10.0 ml.
14-5		residue	30.0 ml.

Fractin (14-5) weighed 39 grams and had a neutralization equivalent of 130. The yield was 78% based on recovery.

Preparation of γ-Methoxy-Butyryl Chloride

To 39 grams of γ-methoxy-butyric acid (14-5) , 40 grams of thionyl chloride were admixed, the resultant, black solution was immediately distilled.

Fraction #	Boiling Range	Weight
17-1	50-170 C.	7.00 gms.
17-2	170-180 C.	25.8 gms.
17-3	residue	

yield; 57% based on 17-2.

Preparation of 1-Diazo-5-Methoxy-2-Pentanone

To one hundred milliliters of annhydrous ether, at room temperature, γ -methoxy-butyryrl chloride (17-2) was added and the resultant solution was slowly added to an annhydrous .5 mole batch of diazomethane etherate, prepared as stated earlier. The addition was accompanied by vigerous evolution of gas. the gas was taken to be methyl chloride. The golden yellow solution was filtered and the ether taken off at room temperature on a water aspirator to give (18-1).

Reaction With Borontrifluoride

The diazoketone (18-1) was dissolved in one hundred milliliters of annhydrous ether. To this solution, 28 grams of borontrifluoride-ether complex were added in four-hundred milliliters of annhydrous ether. This addition was accompanied by the slow evolution of nitrogen. The resulting solution was washed three times with forty milliliters of water and then with forty milliliters of 30% sodium bicarbonate solutionnto give (18-2).

Preparation of γ-Methoxy-Butyric Acid

To one liter of absolute methanol, 94 grams of metallic sodium were added followed by 350 grams of butyrolactone. The mixture was stirred at 79 C. under reflux for 24 hours and worked up as given earlier to yield 10 grams of the above boiling from 105-115 C. at 12mm. The fraction was denoted (20-2) and had a neutralization equivalent of 127, yield; 2.1%.

Preparation of γ-Methoxy-Butyryl Chloride

To (20-2) 11.0 grams of thionyl chloride were added and the mixture fractionated as follows. (1 atm.)

Fraction #	Bath Temperature	Head Temperature	Volume
21-1	2o-2oo C.	20-169 C.	5 ml.
21-2	200-210 C.	170-178 C.	15 ml.
21-3	210-22o C.	178-182 C.	6 ml.

Fractions (21-2)and (21-3) were combined and their neutralization equivalent showed 95.8% purity, yield; 74%.

Preparation of 1-Diazo-5-Methoxy-2-Pentanone

To a previously prepared .5 mole batch of diazomethane in ether, (21-2) and (21-3) were added having first been dissolved in 30 milliliters of annhydrous ether. The steady evolution of a gas was noted. The mixture was let stand for 24 hours, filtered and the ether taken off at room temperature. The volume of the solution was reduced to one half its original size.

Reaction With Borontrifluoride

To the above diazoketone, 18 grams of borontrifluoride-

ether complex were added slowly. The profuse evolution of nitrogen was noted. After standing 20 minutes the reaction mixture was extracted with fifty millliliters of water followed by fifty milliliters of 30% sodium bicarbonate solution. The resulting ethereal solution was filtered through annhydrous sodium sulfate to give (23-1).

Samples (18-2) and (23-1) were stripped of ether on a fractionating column and fractionaly distilled separately. The results follow:

Fractional Distillation of (23-1) (12 mm.)

Fraction#	Bath Temperature	Head Temperature	Volume
	100 C.	50 C.	1 st. drop
24-1	100-125 C.	50-70 C.	1 ml.
24-2	125-135 C.	70-80 C.	10 ml.
24-3	135-150 C.	80-94 C.	5 ml.

Fractional Distillation of (18-2)

Fraction#	Bath Temp.	Head Temp.	Volume	Pressure
24-4	65-100 C.	33-60 C.	1 st.drop	1 atm.
24-5	100-120 C.	60-70 C.		"
24-6	120-200 C.	70-76 C.		"
24-7	(contents of cold trap)			
24-8	20-100 C.	20-59 C.		30 mm.
24-9	100-145 C.	59-80 C.		"
24-10	145-200 C.	80-86 C.		"
24-11	(contents of cold trap)			

Results obtained by virtue of the vapor phase chromatograph indicated that fractions (24-6), (24-9) and (24-10) were generally free from more than one component. The other fractions needed further separation. Because of the small quantities

of these fractions the only feasible method would be column chromatography or, preferrably, vapor phase chromatography.

The infrared spectra of (24-9) and (24-10) were similiar. Both showed strong carbonyl absorption and faint but definite ethoxy absorption. Sample (24-10) showed, furthermore, two distinct carbonyl peaks. Presumably the hydroxyl group had shifted a carbonyl peak upwards in frequency. There was a marked increase in hydroxy absorption in going from (24-9) to (24-10). The spectra of (24-6) gave strong hydroxy indications. This may be an indication of enolization of the cyclic compound.

Samples (24-8) and (24-9) yielded 2,4-dinitrophenylhydrazine derivatives. To one millimole of 2,4-dinitrophenylhydrazine reagent in ethanol, 50 drops of each were added. Sample (24-8) gave 130 milligrams of product, (24-9) gave 14 milligrams. The derivatives were initially crystallized from ethanol, redissolved in boiling ethanol and recrystallized. They were numbered (25-1) and (25-2) respectively and melted at 197 C. and 107-108 C..

Ten microliter samples of the preceeding fractions were analyzed on a Perkin-Elmer vapor phase chromatograph equipped with a type R column. Assuming the following increasing order of retention time for the expected compounds;

(1) 3-keto-tetrahydropyrane

(2) 1-fluoro-5-methoxy-2-pentanone

(3) 1-ethoxy-5-methoxy-2-pentanone

(4) 1-hydroxy-5-methoxy-2-pentanone

the following results were obtained.

Fact. #	Temp.	Retention time	Peak size	Composition
24-1	110	2.8 min.	major	ether
		3.8 "	intermediate	cyclic compound
24-2	110	2.0 "	minor	ether
		2.5 "	minor	ether
		3.9 "	intermediate	ether
		4.0 "	intermediate	cyclic compound
		8.3 "	major	fluoro Ketone
		10.5 "	major	ethoxy ketone
24-3	110	1.4 "	minor	ether
		2.0 "	minor	ether
		2.5 "	minor	ether
		3.5 "	major	cyclic compound
		8.0 "	major	fluoro ketone
		9.9 "	major	ethoxy ketone
ether	112	3.4 "		
24-4	112	3.4 "	major	ether
24-6	112	4.0 "	major	cyclic ketone
		7.4 "	major	fluoro ketone
		10.2 "	major	ethoxy ketone
24-8	184	1.0 "	major	ether
		7.8 "	minor	?
		9.8 "	major	ethoxy ketone
		12.8 "	major	hydroxy ketone

Fract. #	Temp.	Retention time	Peak size	Composition
24-9	184	1.1 min.	major	ether
		9.6 "	major	ethoxy ketone
		12.8 "	minor	hydroxy ketone
24-10	184	1.2	major	ether
		9.6	major	ethoxy ketone
		12.7	minor	hydroxy ketone

Summary and Suggestions

Of the two methods tried for the synthesis of γ-methoxy-butyric acid , methoxylation was best effected with sodium methoxide. Formation of the acid chloride is accomplished easily with thionyl chloride. Best yields were obtained with reflux periods not in excess of ten minutes . The acid chloride should be distilled at , or not too much lower than, one atmosphere pressure due to its volatility.

The borontrifluoride - diazoketone reaction can be followed effectively by collecting the nitrogen evolved during the course of reaction.

The ketones listed earlier as predicted were not found in a thorough search of the literature. Therefore, no primary information was obtained as to their properties. Most of the following conclusions depend on assumptions made earlier as to the order of boiling and retention time and not on any isolation of products.

The infrared spectra and vapor phase analysis of certain fractions seem to indicate the presence of the ethoxy and hydroxy ketones in the higher boiling fractions. Indications of the cyclic and fluoro ketones point to their presence in the low boilers.

Several methods remain untried for synthesizing the methoxy acid. Among these the best prospect from the standpoint of side products is one reminiscent of the malonic ester synthesis.

In future work, more should be done along the lines of quantative collection of the nitrogen evolved upon addition of borontrifluoride to the diazoketone. Data of this nature can lead to a calculation of the % reaction and would also be useful in looking into the reaction kinetics.

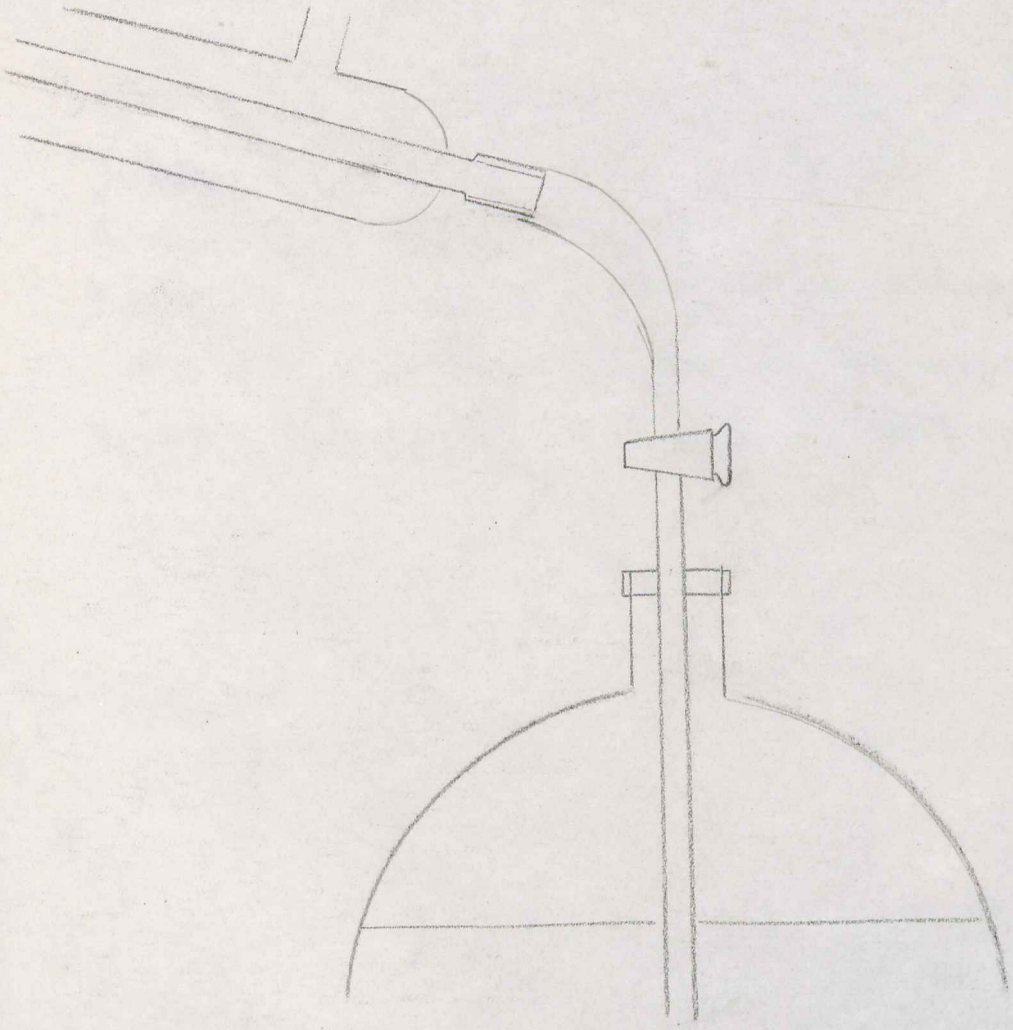


Fig. 1

Bibliography

1.Bose, A.K and Yates, P.; J. Am. Chem. Soc. 74, 7403 (1952)

2.Elderfield, R.C., Kuch, G.A. and Marshall, E.R. ; J. Organic Chem. 7 , 444-456 (1942)

3.Marshall, J. and Walker, J.; J. Chem. Soc. , Part I, 467-475 (1952)

4.Moore, J.A. and Sheffer, H.E. ; J. Organic Chem.,28 (1963)

5.Reppe, Walter et.al. ; Ann. 596, 1-5 (1955)

6.Wolff, L.; Ann. 325, 125 (1902)

7.Gould, E.S. , Mechanism and Structure In Organic Chemistry, 627,Holt, Reinhart and Winston, New York (1959)

8. Arndt, F. and Eistert,; Ber. 68, 200(1935)