

THE USE OF α -HALOAMIDES IN THE REFORMATSKY REACTION

By

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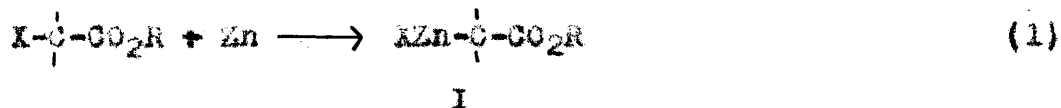
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INTRODUCTION

During a search for better mosquito repellents, it became desirable to prepare certain hydroxyacides. The Reformatsky (2) reaction therefore was investigated as a method of preparing hydroxyacides. The work was begun under a contract recommended by NDRC between the University of Maryland and the Office of Scientific Research and Development. Five compounds were prepared while the author was engaged on the above-mentioned contract. After the contract terminated a study of the Reformatsky reaction involving α -haloacides was continued. The results of the completed study are included in the present thesis.

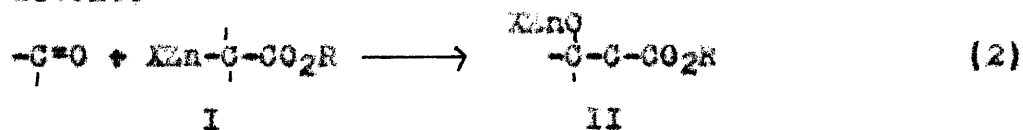
In 1887, Reformatsky (16) reported a condensation of acetone with ethyl iodoacetate in the presence of zinc. Since that time the reaction which takes place between a carbonyl compound such as an aldehyde, a ketone, or an ester and an α -haloester has become known as the Reformatsky reaction. Reformatsky's procedure eliminates the necessity of isolating an organozinc compound. A new carbon-carbon bond is formed and it seems that the following steps take place (17).

1. Formation of an organozinc halide.

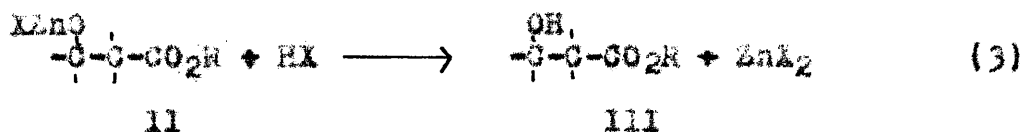


(X represents Cl, Br, I; R is an alkyl group)

2. Addition to the carbonyl group of the aldehyde or ketone.



3. Decomposition by dilute acids.



Thus an aldehyde or a ketone leads to a β -hydroxyester (III) as the final product. Subsequent or simultaneous dehydration may produce an unsaturated ester. When an ester is used in place of an aldehyde or ketone, the product may be a β -ketoester. It is also possible for the carbonyl group of the β -ketoester to react further with the organozinc halide.

The organozinc complexes parallel the intermediates formed in the well-known Grignard reaction, indeed, magnesium may even be substituted for zinc in this reaction (20, 21). Since Grignard reagents cannot be prepared from α -haloesters and magnesium alone, the Reformatsky reaction offers a method which is equivalent to a Grignard reaction for α -haloesters.

The order of reactivity of carbonyl compounds in the Reformatsky reaction is RCHO , H_2CO , $\text{RCO}_2\text{C}_2\text{H}_5$. The order of reactivity of the haloacetates is $\text{ICH}_2\text{CO}_2\text{C}_2\text{H}_5$, $\text{BrCH}_2\text{CO}_2\text{C}_2\text{H}_5$, $\text{ClCH}_2\text{CO}_2\text{C}_2\text{H}_5$. Since α -chloroacetic esters often react slowly or not at all and α -iodoesters are not readily available, most Reformatsky reactions have been carried out with bromoesters.

By use of the Reformatsky reaction it is possible to prepare β -hydroxyesters, the corresponding unsaturated esters and acids. The procedure is also a valuable method of lengthening the carbon chain. By proper choice of reactants it is possible to obtain a chain with various degrees of branching.

DISCUSSION

At the outset of the work, a literature search revealed no general method of preparing N,N-disubstituted- α -bromoamides in good yields. Since these amides were required in fairly large quantities, it was necessary to devise a suitable method of preparation. Miller and Johnson (15) reported a preparation of N,N-diethylbromoacetamide in twenty percent yield by condensing diethylamine in aqueous alkali with bromoacetyl bromide. By adding two moles of an ethereal solution of diethylamine to ethereal solution of bromoacetyl bromide cooled to -15° , we have been able to obtain consistently yields in excess of sixty-five percent; other bromoamides and chloroamides were obtained in yields of sixty percent or better by the use of the same general procedure. All of the α -bromoamides were strongly lachrymatory and sternutatory.

Bischoff (5) reported the preparation of N-methyl- α -bromoacetanilide and N-methyl- α -chloroacetanilide for which he has recorded melting points of 69° and 48° respectively. In the preparation of these compounds in this laboratory, the melting points were the reverse of the ones he reported, Jacobs and Heidelberger (12) prepared N-methyl- α -chloroacetanilide and reported a melting point of 70° . Grothe (10) also reports a melting point of 70° for N-methyl- α -chloroacetanilide. No other

physical constants could be found for N-methyl- α -bromoacetanilide, therefore this product was analyzed for bromine, carbon, and hydrogen. The analytical data were good. 4-ethyl-3-hydroxy-N-methylacrylanilide was obtained in good yield from the condensation of N-methyl- α -bromoacetanilide with 2-ethylhexaldehyde in the presence of zinc. The foregoing evidence indicates that a typographical error may have been made in recording the melting points of Bischoff's products.

Some α -chloroamides were prepared by the same general methods. These amides gave low yields when used in the Reformatsky reaction. Since the chloroamides are as difficult to prepare as the bromoamides there seems to be no particular advantage in their use.

Turnings of an alloy composed of eight percent copper and ninety-two percent zinc were used exclusively. The turnings were washed free of cutting oil and were subjected to no other cleaning. The oil free turnings seemed to have no oxide layer after standing one year and after this time the zinc seemed to be fully as active as when freshly prepared. This form of zinc does not need to be cleaned before each reaction; it seems worthwhile, therefore, to prepare this alloy if many Reformatsky reactions are contemplated.

The longest acyl group contained in any of the α -bromoamides used was that of N,N-diethyl- α -bromocaproamide. The condensation of this amide with 2-ethylbutyraldehyde yielded forty percent of the expected hydroxy amide. No amides with branched acyl groups were investigated. The largest alkyl

group, substituted on the amido nitrogen, was that of N,N-(mixed) diacylbromoacetamide. The hydroxy amide was produced in sixty-five percent yield when N,N-(mixed)diacylbromoacetamide was condensed with 2-ethylbutyraldehyde.

The ketones investigated fall into four categories; aliphatic, mixed aliphatic and aromatic, aromatic, and saturated cyclic. The cyclic ketones are discussed as a separate group because they behave somewhat differently from the other ketones. The other three categories are discussed together.

Cyclic ketones in general appeared to form a more insoluble zinc complex than any other carbonyl compounds that were investigated. Unless high speed stirring is used, this zinc complex will adhere to the metallic zinc with a resultant lowering of yields. It is advisable to use more solvent for this group than is necessary in any other. Cyclohexanone and methylcyclohexanone gave reasonably good yields in all cases but cyclopentanone gave very poor yields.

In four different attempts to condense cyclopentanone with a α -bromoamide, the yields were never over fourteen percent of the calculated amount. In one run where magnesium was substituted for zinc, only an unidentified tar was isolated.

The largest noncyclic ketone that was used was benzophenone. This ketone was treated with N,N-diethylbromoacetamide in the presence of zinc to yield the corresponding hydroxy amide in over fifty percent yield of the calculated amount. This again shows the applicability of the reaction

for the higher members of the homologous series.

In order to study steric effects in this reaction, a series of experiments using the same anhydride with methyl isopropyl ketone, diisopropyl ketone and pinacolone were carried out. N,N-Diethylbromosuccinimide was used in each case. The conditions of the experiments were duplicated as closely as possible. One would predict the order of increasing reactivity to be: diisopropyl ketone, pinacolone, and methyl isopropyl ketone. However, the following yields were obtained respectively, 39, 69, and 55 percent of the calculated amounts. The apparent disagreement from the expected result might be due to loss in washing due to differences in solubility. In a similar experiment that was carried out at a different time with no attempt to duplicate conditions exactly, methyl propyl ketone yielded fifty-two percent of the expected hydroxy anhydride. It is of interest to note that the hydroxy anhydride was the product when diisopropyl ketone was used in this reaction. Conant and Blatt (9) reported reduction of the carbonyl by the addition of the Grignard reagent to diisopropyl ketone in every case except when methyl magnesium iodide was used. By use of the Reformatsky technique we have a means of adding a fairly large organometallic compound to the carbonyl group without reduction. A search of the literature revealed no instance of the use of the Reformatsky reaction with diisopropyl ketone.

Three different experiments were run to test the applicability of α -chloroacides in the reaction. In the condensation of methyl propyl ketone with N,N-diethylchloroacetaide and N,N-diethylbromoacetaide, the respective yields of hydroxy acids were 34% and 52% of the calculated quantity. The treatment of 4-methylcyclohexanone with N,N-diethylchloroacetaide and N,N-diethylbromoacetaide resulted in yields of 32% and 59% of hydroxy acid respectively. Finally the condensation of 2-ethylhexaldehyde with N-methyl- α -chloroacetaide and N-methyl- α -bromoacetaide gave yields of 24% and 70% respectively, of the calculated quantities. This indicates that chloroacides will condense in this reaction but certainly their use offers no advantage.

Several attempts to carry out the Reformatsky reaction with furfural met with failure. The only product obtained was a high boiling oil which decomposed rapidly on standing. No sample pure enough for analysis was obtained. In one case, eighty-five percent of the starting acid was recovered unchanged. This failure of the reaction is strange in the light of the fact that furfural has been used in the usual Reformatsky reaction.

In one experiment, the condensation of phenyl acetaldehyde with N,N-(mixed)dialkylbromoacetaide was attempted. Only a small amount of an unidentified tar was isolated.

Nine ketones were investigated and all of them yielded the expected hydroxy acid. Four aldehydes produced the expected hydroxy acid but anisaldehyde yielded the corresponding

unsaturated acids in two experiments involving different α -bromoacids.

In the hope of preparing a solid product, cinnamaldehyde was condensed with N-ethyl- α -bromoacetanilide. A solid product was obtained that was isolated and purified without employing distillation. Since dehydration would give a system with five conjugated double bonds, the expected compound might well have been too unstable to undergo distillation. Although the analysis was in error by eight-tenths of one percent the product was undoubtedly the hydroxy acid.

Attempts to dehydrate N-ethyl-(3-hydroxy-5-phenyl-4-penten)anilide by the use of formic acid yielded an oil which could not be induced to crystallize. Treatment of this compound with bromine did not yield a crystalline product.

The other aldehydes used, benzaldehyde, 2-ethylbutyraldehyde, and 2-ethylhexaldehyde, reacted as expected.

N,N-Diethyl- β -phenylcinnamamide was prepared from N,N-diethyl- β,β -diphenylhydroacrylamide by dehydration with ninety-eight percent formic acid. Dibromides were prepared from the unsaturated acids obtained from anisaldehyde.

After using N,N-disubstituted- α -bromoacids in the Reformatsky reaction, an N-monosubstituted acid was investigated. Reaction did not take place in the expected manner. α -Bromoacetanilide was treated with acetophenone and with 2-ethylhexaldehyde according to the usual Reformatsky technique. Acetanilide was the only product isolated from either experiment.

In the case of 2-ethylhexaldehyde, sixty-one percent of the starting amide was recovered as acetanilide. The acetanilide was identified by carbon and hydrogen analysis and by a mixed melting point with pure acetanilide. In another attempt using benzaldehyde, the α -bromoacetanilide was recovered unchanged.

The reduction of α -bromoacetanilide to acetanilide in the Reformatsky reaction has not been investigated. It does seem probable that zinc was the reducing agent.

The primary purpose of the synthetic work was to investigate the scope of the new application of the Reformatsky reaction. The procedures were adapted from similar experiments described for α -bromoesters. In many cases yields reported are those obtained from only one experiment. In a few cases conditions were varied systematically to find those best suited to the reactants involved.

In a series of three duplicate experiments for the preparation of N,N-diethyl- β -phenylhydraacrylamide the following solvent mixtures were used: 30 ml. of ether in 50 ml. of benzene, 80 ml. of benzene, and 30 ml. of toluene in 50 ml. of benzene. The respective yields were 32%, 58%, and 37% of the calculated amounts. Since the mixture was refluxed in each case, the yield seemed to be quite dependent on the temperature at which the reaction was carried out. In a similar study of the preparation of N,N-diethyl-1-hydroxy- α -N-ethylcyclohexanecetamide, a similar result was obtained. The

solvent mixtures used were; 80 ml. of benzene and 80 ml. of toluene, 40 ml. of benzene and 120 ml. of toluene, and 160 ml. of toluene. In this case the yields were 14.5%, 30%, and 18% respectively of the calculated quantity. From these experiments it may be concluded that if any of the yields reported are maxima it is indeed fortuitous.

It is of interest to compare the yields of similar carbonyl compounds using bromoesters and bromoamides. Table I gives such a comparison. The values for the bromoesters are those given by Shriner (2). It will be noted that in general the yields are somewhat lower for bromoamides than for bromoesters.

Four of the compounds prepared in this laboratory were tested for their mosquito repellency by the Bureau of Entomology and Plant Quarantine, Orlando, Florida. The results of these tests are given in Table II. By convention, liquids having a repellent time in excess of 179 minutes against *Aedes Aegypti*, or 119 minutes against *Anopheles Quadrimaculatus* are considered repellent. Two of the compounds tested exceeded the minimum value against *Aedes*.

TABLE I. Comparison of the Reformatsky Reaction Using α -Bromoesters and α -Bromoamides.

Bromoesters		Bromoamides	
Carbonyl Compound	Yield	Carbonyl Compound	Yield
2-Methylpropionaldehyde	41%	2-Ethylbutyraldehyde	65%
Heptaldehyde	54%	2-Ethylhexaldehyde	76%
Furfural	61%	Furfural	0
Benzaldehyde	78%	Benzaldehyde	58%
Acetone	50%	Methyl ethyl ketone	48%
Cyclohexanone	74%	Cyclohexanone	60%
4-Methylcyclohexanone	87%	4-Methylcyclohexanone	59%
Benzophenone	75%	Benzophenone	53%

TABLE II. Results of Repellent Testing

Compound	Result of Testing					
	Aedes			Anopheles		
	No. of tests	Range in minutes	Ave.	No. of tests	Range in minutes	Ave.
1-Hydroxy-N,N-disopropylcyclohexanecarboxamide	6	171-392	265	6	29-56	39
2-Hydroxy-2-methyl-N,N-dipropylvaleramide	6	209-385	296	6	27-69	43
N,N-Diethyl-2-phenylhydracrylamide	2	70-139	105	2	46-50	48
N,N-Diethyl-1-hydroxycyclohexanecarboxamide	2	58-113	86	2	27-28	28

EXPERIMENTAL

This section of the thesis is divided into three divisions: The Preparation of α -Haloamides, The Reformatsky Reaction, and General Experiments.

The Preparation of α -Haloamides

The preparation of different α -haloamides involved modifications of a general procedure. The general procedure will be given and each separate experiment will be described in condensed form with any variations that were used. The preparation of α -haloamides was carried out in a one-liter three-necked flask fitted with a Hershberg stirrer, a dropping funnel with gas outlet, and a low temperature thermometer extending into the solution. The flask was immersed in a mixture of dry ice and isopropanol contained in a one gallon wide-mouthed Dewar flask. An ethereal solution of the appropriate α -bromoacyl bromide was placed in the flask and the solution was cooled to -15° . An ethereal amine solution was then added through the dropping funnel at such a rate that the temperature did not exceed -10° . The reaction mixture was dissolved in water and the organic layer was separated. The organic layer was washed successively with dilute phosphoric acid, dilute potassium carbonate solution, and finally with concentrated sodium chloride solution until neutral. It is important to wash the ethereal solution free of amine hydrohalide at this point. The solution was dried over magnesium sulfate and the solvent was

removed by distillation. The product was distilled or recrystallized.

Preparation of N,N-Diethylbromoacetamide. To a solution of 151 g. (0.75 mole) of bromoacetyl bromide in 450 ml. of dry ether, was added 132 g. (1.5 moles) of diethylamine in 150 ml. of ether. The reaction mixture was treated in the standard manner. The product was a water white amide that was distilled; it boiled at 89-90°/1.0 mm. (15). The yield was 107 g. (74 percent of the calculated amount).

Preparation of N,N-Dipropylbromoacetamide. The preparation of N,N-dipropylbromoacetamide was carried out using 100 g. (0.5 mole) of bromoacetyl bromide in 450 ml. of dry ether and 111 g. (1.1 moles) of dipropylamine in 150 ml. of dry ether in the usual manner. The amide distilled at 98-100°/2.0 mm. The yield of water-white product was 89 g. (80 percent of the theoretical amount). This compound was not analyzed. The material was condensed with methyl ethyl ketone to yield the expected hydroxamide in 48 percent of the calculated quantity.

Preparation of N,N-Diisopropylbromoacetamide. This compound was prepared from 151 g. (0.75 mole) of bromoacetyl bromide in 450 ml. of dry ether and 152 g. (1.5 moles) of diisopropylamine in 150 ml. of ether. The experiment was conducted in the usual manner. The solvent was removed by distillation and the product was distilled; it boiled at 70-71°/0.3 mm. The yield was 75 g. (45 percent of the theoretical quantity). After standing for several days the

N,N-diisopropylbromoacetamide solidified. The solid was recrystallized from petroleum ether (30-60°) and the purified material melted at 65.3-66.5°.

Anal. Calc'd. for $C_9H_{18}BrNO$: C, 43.24; H, 7.21. Found: C, 43.40; H, 7.32.

Preparation of N,N-(mixed)Dianylbromoacetamide. The preparation of N,N-dianylbromoacetamide was carried out by treating 100 g. (0.5 mole) of bromoacetyl bromide in 450 ml. of dry ether with 173 g. (1.1 moles) of mixed dianylamine* in 150 ml. of dry ether. The solvent was removed by distillation and the product distilled; it boiled at 128-129°/0.7 mm. The yield was 99 g. (71 percent of the calculated amount).
Anal. Calc'd. for $C_{12}H_{24}BrNO$: C, 51.80; H, 8.03. Found: C, 51.57; H, 8.42.

Preparation of N,N-Diethyl- α -bromopropionamide. This substance was prepared from 200 g. (0.98 mole) of α -bromopropionyl bromide in 450 ml. of dry ether and 150 g. (2.05 moles) of diethylamine in 150 ml. of ether. The reaction was carried out in the usual manner. The product was a water white liquid that was distilled; it boiled at 74°/0.2 mm. The yield was 157 g. (77 percent of the theoretical amount).
Anal. Calc'd. for $C_7H_{14}BrNO$: Br, 38.46. Found: Br, 38.83.

*The amine was Sharples technical grade of mixed dianylamine. This amine was dried and distilled, the portion that boiled at 115-116°/15 mm. was used.

Preparation of N,N-Diethyl- α -bromocaproamide. N,N-Diethyl- α -bromocaproamide was prepared by the standard method by treating 172 g. (0.81 mole) of α -bromocaproyl chloride (14) in 450 ml. of dry ether with 120 g. (1.05 moles) of diethylamine in 150 ml. of ether. The product was distilled; it boiled at 77-78°/0.1 mm. The yield of water-white amide was 112 g. (56 percent of the theoretical amount).

Anal. Calc'd. for $C_{10}H_{20}BrNO$: C, 48.00; H, 8.00. Found: C, 47.93; H, 7.97.

Preparation of N-methyl- α -bromoacetanilide. Bischoff (5) reported a preparation of N-methyl- α -bromoacetanilide for which a melting point of 69° is given.

Our attempts to duplicate his work resulted in a product which melted at 46.8-47.3°. This substance was analyzed for bromine, carbon, and hydrogen.

Anal. Calc'd. for $C_9H_{10}BrNO$: C, 47.37; H, 4.39; Br, 35.07. Found: C, 47.42, 47.30, 47.49; H, 4.44, 4.74, 4.82; Br, 34.98.

Preparation of N-ethyl- α -bromoacetanilide. This compound was prepared from 100 g. (0.5 mole) of bromoacetyl bromide in 450 ml. of dry ether and 135 g. (1.1 moles) of ethylaniline in 150 ml. of dry ether. The reaction mixture was worked up as usual. The solvent was removed by distillation and the product distilled; it boiled at 125-127°/0.2 mm. The yield was 68 g. (73 percent of the theoretical quantity).

Anal. Calc'd. for $C_{10}H_{12}BrNO$: C, 49.59; H, 4.97. Found C, 49.49; H, 5.09.

Preparation of N,N-Diethylchloroacetamide. This preparation was carried out by treating 84 g. (0.75 mole) of chloroacetyl chloride in 450 ml. of dry ether. The diethylamine hydrochloride was removed by filtration. The solvent was removed by distillation and the amide distilled; it boiled at $117-118^{\circ}/17$ mm. Jacobs and Heidelberger (13) give a boiling point of $126.5-128.5^{\circ}/21$ mm. for this compound. The yield was 90 g. (80 percent of the theoretical amount).

Preparation of N-Methyl- α -chloroacetanilide. This compound was prepared in an analogous manner to N-methyl- α -bromoacetanilide from 57 g. (0.5 mole) of chloroacetyl chloride in 450 ml. of dry ether and 120 g. (1.1 moles) of methyl aniline in 150 ml. of ether. The product was recrystallized from petroleum ether ($60-80^{\circ}$); it melted at $69-70^{\circ}$ (12). The yield was 74 g. (80 percent of the theoretical amount).

Preparation of α -Bromoacetanilide. This amide was prepared by the method of Abenius (1).

The Reformatsky Reaction

The experiments are given in the order of increasing complexity of the carbonyl compounds. All the aldehydes precede the ketones.

When quantities of reactants on the order of a quarter of a mole were used, the Reformatsky reaction was carried

out in a 500-ml., three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. The dropping funnel and reaction flask were protected from moisture in the atmosphere by drying tubes. A crystal of iodine and the proper quantity of zinc-copper alloy was introduced into the flask and the apparatus was flamed with a luminous flame while a slow stream of air was drawn through it, whereupon the apparatus was allowed to cool. A solution of α -haloamide and the carbonyl compound was prepared. About fifteen ml. of this solution was added to the flask, stirring was started and the reaction mixture was heated under reflux by means of a 'Glastol' heating mantle until the reaction started. The reaction usually started within fifteen minutes and if the reaction became too vigorous the flask was cooled in a water bath. After the initial reaction had subsided, the remainder of the solution was added at such a rate that the reaction mixture refluxed gently. The addition was usually complete in one hour and the reaction mixture was heated under reflux for one more hour. The reaction mixture was allowed to cool to room temperature and the zinc complex was hydrolyzed with excess, cold, ten percent sulfuric acid; usually about two hundred ml. were required. The copper and excess zinc were removed by filtration and the organic layer was washed with five percent sulfuric acid, five percent potassium carbonate, and finally with saturated sodium chloride solution until the organic layer was neutral. The solution was dried over magnesium sulfate and the solvent was removed by distillation. The product was then purified by distillation or recrystallization.

Melting points are corrected.

Densities of the liquids were determined at 25° in a pycnometer having a volume of about four-tenths of a milliliter. Refractive indices were determined at 25° for the D-line of sodium. The molar refraction was determined from the equation of Lorentz and Lorenz,

$$M_r = \frac{n^2 - 1}{n^2 + 1} \cdot \frac{M}{d}$$

where M_r is the molar refraction, n is the refractive index, M is the molecular weight, and d is the density. The equation gives the observed molar refraction. The molar refraction was calculated by a summation of atomic refractivities, using data of Luvers and Eisenlohr for the D-line of sodium as given by Gilman (9). The value for tertiary amino nitrogen was used for the N,N-disubstituted amide nitrogen.

Preparation of N,N-(mixed)Diethyl-4-ethyl-3-hydroxyvaleramide. A solution of 49 g. (0.17 mole) of N,N-(mixed)diethylbromacetamide and 20 g. (0.20 mole) of 2-ethylbutyraldehyde* in 75 ml. of dry benzene and 20 ml. of absolute ether was condensed in the usual manner by means of 14.3 g. (0.20 atom) of zinc-copper alloy. The solvent was removed by distillation and the product distilled; it boiled at 144-146°/0.3 mm. The yield of water-white liquid was 33 g. (65 percent of the calculated amount).

A portion was purified for analysis by distillation; the fraction which distilled at 142-143°/0.2 mm. was taken. The

*Eastman Kodak technical 2-ethylbutyraldehyde was fractionated through a 70 cm. helix-packed column. The fraction that was used had a boiling point of 116-117°.

density and refractive index were determined and the molar refraction was calculated. D_{25}^{25} , 0.9105; N_D^{25} , 1.4594; $M_r(\text{obs.})$, 89.80; $M_r(\text{cal.})$, 90.81.

Anal. Calc'd. for $C_{16}H_{37}NO_2$: C, 72.24; H, 12.37. Found: C, 71.81, 71.88; H, 12.23, 12.44.

Preparation of 2-Butyl-N,N,4-triethyl-3-hydroxycaproamide. The preparation of this compound was carried out in the usual manner. The quantities of reactants used were 45 g. (0.18 mole) of N,N-diethyl- α -bromocaproamide and 20 g. (0.20 mole) of purified 2-ethylbutyraldehyde in 100 ml. of dry benzene. The product was distilled, it boiled at 124-125°/0.3 mm. The yield of slightly yellow liquid was 21 g. (43 percent of the theoretical quantity). 12

A portion was further purified by distillation. The fraction that was analyzed distilled at 109-110°/0.1 mm. The density and refractive index were determined on this fraction and the molar refraction calculated. D_{25}^{25} , 0.9303; N_D^{25} , 1.4035; $M_r(\text{obs.})$, 80.37; $M_r(\text{cal.})$, 81.57.

Anal. Calc'd. for $C_{16}H_{33}NO_2$: C, 70.85; H, 12.18. Found C, 70.06, 70.29; H, 12.24, 12.38.

Attempted Condensation of 2-Ethylhexaldehyde with α -Bromoacetanilide. A 500-ml. three-necked flask was fitted with a reflux condenser and stirrer. A crystal of iodine and 14.3 g. (0.2 atom) of zinc-copper alloy were added and the flask was flamed with a luminous flame while a slow stream of air was drawn through the apparatus.

A solution of 39 g. (0.18 mole) of α -bromoacetanilide and 25.5 g. (0.2 mole) of 2 ethylhexaldehyde* in 350 ml. of dry hot benzene was prepared. Twenty-five ml. of the hot solution was added to the flask and the mixture was heated under reflux until the reaction started. After the initial reaction had subsided the remainder of the solution was added in 25-ml. portions at such a rate that the reaction mixture boiled gently. After all the reactants had been added, the reaction mixture was heated under reflux for one hour and then allowed to cool. The reaction mixture was worked up in the usual manner. After most of the solvent had been removed by distillation, petroleum ether (60-80°) was added until a slight turbidity was noted. The solution was allowed to cool. Fifteen grams (accounting for 61 percent of the bromo-compound) of white powdery crystals precipitated. The melting range of the crude product was 102-108°. After four recrystallization from benzene the product melted at 113.5-115° (uncorr.) A mixed melting point with acetanilide gave no depression. A sample was dried and analyzed. The analytical data checks very closely for acetanilide.

Anal. Calculated for C_9H_9NO : C, 71.11; H, 6.67. Found: C, 71.05, 71.16; H, 6.82, 6.86.

* The 2-ethylhexaldehyde was the technical product of the Paragon Testing Laboratories. The aldehyde was purified by fractionating it through a 70 cm. helix-packed column. The fraction used was distilled; it boiled at 103-105°.

Preparation of 4-ethyl-3-hydroxy-N-methylacetanilide.

Method I. This condensation was carried out between 41 g. (0.18 mole) of N-methyl- α -bromoacetanilide and 25.5 g. (0.2 mole) of purified 2-ethylhexaldehyde in 80 ml. of dry benzene and 20 ml. of dry ether using 14.3 g. (0.2 atom) of zinc-copper alloy in the usual manner. The solvent was removed by distillation and the amide distilled; it boiled at 141-143^o/0.6 mm. The yield of slightly colored liquid was 38 g. (76% of the theoretical amount).

A portion was purified for analysis. The fraction which distilled at 135-136^o/0.3 mm. was taken. The density and refractive index were determined and the molar refraction was calculated. D_{25}^{25} , 0.9959; n_D^{25} , 1.5079; $M_r(\text{obs.})$, 82.91 $M_r(\text{cal.})$, 81.58.

Anal. Calc'd. for $C_{17}H_{27}NO_2$: C, 73.65; H, 9.75. Found: C, 74.29, 74.01; H, 9.80, 10.08.

Method II. This experiment differed from Method I in that N-methyl- α -bromoacetanilide was replaced by N-methyl- α -chloroacetanilide. The solvent for this reaction was 60 ml. of dry benzene and 60 ml. of dry toluene. The product was distilled; it boiled at 144-146^o/0.6 mm. and had a refractive index of 1.5078 at 25^o. The yield was 12 g. (24% of the calculated amount).

Attempted Condensation of Furfural with α -Bromoamides.

Method I. The reaction was investigated using 43 g. (0.22 mole) of N,N-diethylbromoacetamide and 24 g. (0.25 mole)

of furfural* in 75 ml. of benzene and 20 ml. of ether. Eighteen grams (0.25 atom) of zinc-copper alloy was used as the condensing agent. The reaction started smoothly and was carried out in the usual manner. The product was a dark red oil that distilled at 128-130°/0.5 mm. The yield was 13 g. This product decomposed rapidly on standing. It was never obtained in a pure enough state for analysis.

Method II. This experiment was similar to that of Method I, except that the zinc complex was decomposed differently.

An attempt was made to decompose the zinc complex with a solution of ammonium chloride but this would not dissolve the complex. Enough hydrochloric acid was then added to the aqueous layer to make it just acid after the complex was decomposed. The organic layer was separated and washed with water until it was neutral. The solution was dried over magnesium sulfate. The drying agent was removed and the solvent removed by distillation. The product from this reaction was distilled; it boiled at 129-130°/0.6 mm. The yield was 11 g. This product was also unstable.

Method III. An attempt to condense 41 g. (0.18 mole) of N-methyl- α -bromoacetamide and 19.2 g. (0.2 mole) of puri-

*The furfural used was obtained from the Laker Oats Company. A benzene solution of furfural was washed with five percent potassium carbonate solution and with water until neutral. The solution was dried over magnesium sulfate. The drying agent was removed by filtration and the furfural distilled; it boiled at 85-86°/60 mm.

fied furfural in 180 ml. of dry benzene with 14.3 g. (0.2 atom) of zinc-copper alloy was made. There was no evidence of any reaction taking place and 35 g. of the N-methyl- α -bromoacetanilide was recovered.

Attempted Condensation of α -Bromoacetaldehyde with Benzaldehyde. A 500-ml., three-necked flask was fitted with a reflux condenser and a stirrer. A crystal of iodine and 9.3 g. (0.13 atom) of zinc-copper alloy were added. The flask was flamed with a luminous flame while a slow stream of dry air was drawn through it.

A mixture of 17 g. (0.12 mole) of α -bromoacetaldehyde, 13.8 g. (0.13 mole) of purified benzaldehyde* and 150 ml. of dry benzene was added to the flask all at once. The mixture was heated under reflux with stirring for one hour. A tar formed during this time that was insoluble in ten percent sulfuric acid solution and in common organic solvents. This product was not further identified.

Preparation of N,N-Diethyl- β -phenylhydracrylamide.

Method I. A solution of 21.2 g. (0.2 mole) of purified benzaldehyde and 35 g. (0.18 mole) of N,N-diethylbromoacetaldehyde in 50 ml. of dry benzene and 30 ml. of dry

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*Paragon Testing Laboratory's chlorine free benzaldehyde was purified in the following manner. The aldehyde was dissolved in benzene and this solution was washed free of acid with five percent potassium carbonate solution, then washed with water until neutral, and dried over magnesium sulfate. The drying agent was removed by filtration and the aldehyde distilled, it boiled at 75-76°/16 mm.

ether was treated in the usual manner with 14.3 g. (0.2 atom) of zinc-copper alloy. The solvent was removed by distillation and the product distilled; it boiled at 137-138°/0.1 mm. The yield of slightly colored liquid was 13 g. (32% of the theoretical amount). The refractive index of this material was 1.5255 at 25°.

A portion of this amide was purified for analysis by distillation. A fraction was used that distilled at 137-138°/0.1 mm. The density and refractive index were determined and the molar refraction was calculated. D_{25}^{25} , 1.060; n_D^{25} , 1.5265; MR (obs.), 64.07; MR (cal.), 63.12. Anal. Calc'd. for $C_{13}H_{19}NO_2$: C, 70.59; H, 8.60. Found: C, 70.04, 70.25; H, 8.68, 8.59.

Method II. This experiment was identical with that of Method I except that 80 ml. of benzene was the solvent. The product was distilled, it boiled at 137-138°/0.1 mm. and it had a refractive index of 1.5258 at 25°. The yield was 23 g. (58 percent of the theoretical amount).

Method III. This experiment duplicated that of Method I except that 50 ml. of dry benzene and 30 ml. of dry toluene was the solvent. The product was distilled, it boiled at 139-140°/0.1 mm. and had a refractive index of 1.5256 at 25°. The yield was 15 g. (37 percent of the calculated quantity).

Attempted Condensation of α -Bromoacetanilide with Benzaldehyde. A 500-ml, three-necked flask was fitted with

a reflux condenser and stirrer. This flask was connected by means of glass tubing to a 500-ml., two-necked flask fitted with a reflux condenser in such a manner that hot liquid could be forced into the reaction vessel.

A crystal of iodine and 14.3 g. (0.2 atom) of zinc-copper alloy were placed in the reaction vessel and the apparatus was flamed. To the two-necked flask was added 21.2 g. (0.2 mole) of purified benzaldehyde, 39 g. (0.2 mole) of α -bromoacetanilide and 300 ml. of dry benzene. This mixture was heated to boiling to effect solution of the amide. About fifty milliliters of the hot solution was forced into the reaction vessel by means of compressed air. The reaction vessel was heated but no reaction took place. All the solution was heated under reflux for three hours; and no reaction took place. Thirty-five grams of α -bromoacetanilide was recovered unchanged.

Attempted Condensation of N,N-(mixed)Dianylbromoacetamide with Phenylacetaldehyde. The condensation of 49 g. (0.17 mole) of N,N-(mixed)dianylbromoacetamide and 24 g. (0.2 mole) of freshly distilled phenylacetaldehyde⁵ with 14.3 g. (0.2 atom) of zinc-copper alloy was tried in a solution of 75 ml. of dry benzene and 20 ml. of absolute ether. A reaction appeared to take place and the reaction mixture

⁵The phenylacetaldehyde used was a fifty percent ethanolic solution of Eastman Kodak's technical product. The ethanol was removed by distillation and a fraction of the aldehyde that distilled at 104°/30 mm. was used.

was worked up in the usual manner. On distillation only low boiling material and about two grams of a tarry residue were obtained. The tar was not identified.

Preparation of N-ethyl-(3-hydroxy-5-phenyl-4-penten)-anilide. Since cinnamaldehyde is oxidized very rapidly by the air and the reaction was fairly sluggish, the usual procedure had to be modified for this preparation.

Thirty grams (excess) of cinnamaldehyde^{*} was dissolved in 75 ml. of benzene. This solution was washed with five percent potassium carbonate solution and then with water until neutral. The solution was dried over magnesium sulfate and the drying agent was removed by filtration. To the benzene solution was added 41 g. (0.17 mole) of N-ethyl- α -bromoacetanilide. About fifteen ml. of this solution was added to the flask containing 14.3 g. (0.2 atom) of zinc-copper alloy and the mixture was heated under reflux until the reaction started. The initial reaction was allowed to subside, and then the remainder of the reactants were added to the boiling reaction mixture. After the addition was complete, the mixture was heated under reflux for one hour. When the zinc complex was decomposed, an additional liter of benzene was required to keep the organic material in solution. The organic layer was separated and washed in the usual manner; a yellow solid remained after the solvent had been

^{*}The cinnamaldehyde was obtained from the Paragon Testing Laboratory.

removed by distillation. The solid crystallized from a mixture (1:4) of benzene and petroleum ether (60-80°) in white needles that melted at 107-109°. The yield was 19 g. (38 percent of the calculated amount).

A portion of the product was purified by recrystallization and the purified material melted at 109-109.5°.

Anal. Calculated for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.13. Found: C, 76.80, 76.54, 77.56; H, 7.14, 7.13, 7.26.

Preparation of N,N-Diethyl- β -anisylacrylamide. A solution of 27.2 g. (0.2 mole) of anisaldehyde* and 33 g. (0.17 mole) of N,N-diethylbromoacetamide in 75 ml. of dry benzene and 20 ml. of dry ether was treated in the usual manner with 14.3 g. (0.2 atom) of zinc-copper alloy. The substance underwent dehydration during its preparation. The product was distilled, it boiled at 167-170°/0.4 mm. The yield was 22 g. (55 percent of the theoretical amount).

A portion of the product was purified for analysis by distillation, and the fraction taken boiled at 144-145°/0.1 mm. The density and refractive index were determined and the molar refraction calculated. D_{25}^{25} , 1.068; n_D^{25} , 1.5902; $M_r(\text{obs.})$, 73.04; $M_r(\text{cal.})$, 68.35

Anal. Calc'd. for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.15. Found: C, 71.40, 71.05; H, 8.09, 8.30.

*The anisaldehyde was obtained from the Paragon Testing Laboratory. This aldehyde was purified by dissolving in benzene and washing the resulting solution with five percent potassium carbonate solution and washing until neutral with water. The solution dried and the solvent was removed. The aldehyde was distilled; it boiled at 92-93°/0.5 mm.

Preparation of N,N-Diisopropyl- β -anisylacrylamide.

This compound was prepared from 36 g. (0.17 mole) of N,N-diisopropylbromacetamide and 27.2 g. (0.2 mole) of purified anisaldehyde in 75 ml. of dry benzene and 20 ml. of dry ether with 14.3 g. (0.2 atom) of zinc-copper alloy in the usual manner. The solvent was removed by distillation and the product was distilled; it boiled at 103-105°/0.4 mm. The yield of yellow oil was 14 g. (30 percent of the calculated amount).

The oil crystallized after standing for several weeks. The substance crystallized in white needles from petroleum ether (30-60°) and melted at 68.7-69.9°.

Anal. Calc'd. for $C_{16}H_{23}NO_2$: C, 73.56; H, 8.81. Found; C, 73.60, H, 9.18.

Preparation of N,N-Dipropyl-3-hydroxy-3-methylvaleramide.

A solution of 49 g. (0.22 mole) of N,N-dipropylbromacetamide and 18 g. (0.25 mole) of methyl ethyl ketone* 100 ml. of toluene and 25 ml. of dry benzene was prepared. This solution was treated with 18 g. (0.25 atom) of zinc-copper alloy in the usual manner. The product was distilled; it boiled at 106-107°/0.5 mm. The yield 22 g (48 percent of the theoretical amount).

A portion was purified for analysis by distillation. A fraction distilling at 95-96°/0.3 mm. was submitted for analysis.

*The ketone was the practical grade obtained from Eastman Kodak Company. This material was purified by fractionation through a 70 cm. helix-packed column and the fraction distilling at 80° was used.

The density and refractive index were determined and the molar refraction calculated from that data. D_{25}^{25} , 0.9327; n_D^{25} , 1.4524; $M_r(\text{obs.})$, 62.18; $M_r(\text{cal.})$, 63.10.

Anal. Calc'd. for $C_{12}H_{25}NO_2$: C, 66.98; H, 11.03. Found: C, 66.54, 66.82; H, 11.73, 11.60.

Preparation of N,N-Diethyl-3-hydroxy-3-methylacetoamide.

Method I. A solution of 43 g. (0.22 mole) of N,N-diethylbromoacetamide and 22 g. (0.25 mole) of methyl propyl ketone* in 125 ml. of dry toluene was prepared. This solution was treated in the usual fashion with 18 g. (0.25 atom) of zinc-copper alloy. The product was distilled, it boiled at 95-97°/0.2 mm. The yield was 23 g. (52 percent of the calculated amount).

A portion was redistilled and the fraction which boiled at 94-95°/0.2 mm. was analyzed. The density and refractive index were determined and the molar refraction calculated. D_{25}^{25} , 0.9402; n_D^{25} , 1.4530; $M_r(\text{obs.})$, 57.74; $M_r(\text{cal.})$, 58.48.

Anal. Calc'd. for $C_{11}H_{23}NO_2$: C, 65.67; H, 11.54. Found: C, 65.47, 65.17; H, 11.57, 11.05.

Method II. In an experiment similar to that of Method I, 33 g. (0.22 mole) of N,N-diethylchloroacetamide was used to replace the N,N-diethylbromoacetamide. The same solvent was used in both cases. The amide from this reaction was distilled; it boiled at 93-95°/0.2 mm. and had a refractive index of 1.4543 at 25°. The yield was 15 g. (34 percent of the calculated amount).

*The ketone was Eastman Kodak's practical grade. This ketone was fractionated through a 70 cm. helix-packed column. The fraction that distilled at 103° was used.

Preparation of N,N-Diethyl-3,4-dimethyl-3-hydroxyvaleramide. A solution of 35 g. (0.18 mole) of N,N-diethylbromoacetamide and 17.2 g. (0.2 mole) of methyl isopropyl ketone (6) in 80 ml. of dry benzene was prepared. The condensation was carried out in the usual manner by means of 14.3 g. (0.2 atom) of zinc-copper alloy. The product was distilled; it boiled at 84-85°/0.3 mm. The yield of water-white liquid was 20 g. (55 percent of the calculated amount).

An analytical sample was prepared by distillation; a fraction which distilled at 74-75°/0.1 mm. was taken. The density and refractive index were determined and from this data the molar refraction was found. D_{25}^{25} , 0.9477; N_D^{25} , 1.4548; M_r (obs.), 57.54; M_r (cal.), 58.48. Anal. Calc'd. for $C_{11}H_{23}NO_2$: C, 65.67; H, 11.54. Found: C, 65.30, 65.13; H, 11.68, 11.51.

Preparation of N,N-Diethyl-3-hydroxy-3,4,4-trimethylvaleramide. A solution of 35 g. (0.18 mole) of N,N-diethylbromoacetamide and 20 g. (0.20 mole) of pinacolone* in 80 ml. of dry benzene was prepared. The condensation was carried out in the usual manner by means of 14.3 g. (0.2 atom) of zinc-copper alloy. The product was distilled, it boiled at 97°/0.6 mm. The yield of water-white amide was 27 g. (69 percent of the theoretical amount).

* This pinacolone was a student preparation made at the University of Maryland. It was purified by distillation through a 70 cm. helix-packed column. A fraction which distilled at 107-108° and had a refractive index of 1.3955 at 22° was used.

A portion was redistilled for purification and a fraction was distilled at $97^{\circ}/0.6$ mm. was analyzed. The density and refractive index were determined from that fraction and the molar refraction was calculated. D_{25}^{25} , 0.9442; n_D^{25} , 1.4577; M_r (obs.), 62.43; M_r (cal.), 64.20.
 Anal. Calc'd. for $C_{12}H_{26}NO_2$: C, 66.66; H, 12.04. Found C, 66.54, 66.29; H, 11.78, 11.71.

Preparation of N,N-Diethyl-3-hydroxy-4-acetyl-3-isopropyl-valeramide. A solution of 35 g. (0.18 mole) of N,N-diethyl-bromoacetamide and 22.8 g. (0.20 mole) of diisopropyl ketone* in 80 ml. of dry benzene was prepared. This was treated by the standard method with 14.3 g. (0.20 atom) of zinc-copper alloy. The product was distilled, it boiled at $108-109^{\circ}/0.6$ mm. The yield was 16 g. (39 percent of the theoretical quantity).

A portion was purified for analysis by distillation and the fraction distilling at $108-109^{\circ}/0.6$ mm. was analyzed. The density and refractive index were determined and the molar refraction calculated. D_{25}^{25} , 0.9520; n_D^{25} , 1.4641; M_r (obs.), 66.36; M_r (cal.), 67.71.

Anal. Calc'd. for $C_{13}H_{27}NO_2$: C, 68.12; H, 11.79. Found: C, 67.51, 67.50; H, 11.90, 11.70.

Preparation of N,N-Diethyl-1-hydroxycyclopentanecetamide.

Method I. A solution of 43 g. (0.22 mole) of N,N-diethyl-bromoacetamide and 21.2 g. (0.25 mole) of cyclopentanone (8) in

* This ketone was the practical grade from Eastman Kodak Company. The material was fractionated through a 79 cm. helix-packed column. The fraction used boiled at $123-125^{\circ}$.

100 ml. of dry benzene was prepared. The condensation was carried out with 18 g. (0.25 atom) of zinc-copper alloy in the usual manner. The product was distilled, it boiled at 100-101°/0.3 mm. The yield of slightly yellow amide was 6 g. (13.5 percent of the theoretical quantity).

A portion was purified for analysis. This fraction distilled at 94-95°/0.1 mm.; its density and refractive index were determined and the molar refraction calculated. D_{25}^{25} , 1.005; n_D^{25} , 1.4743; M_r (obs.), 55.66; M_r (cal.), 56.28. Anal. Calc'd. for $C_{11}H_{21}NO_2$: C, 66.33; H, 10.56. Found: C, 65.85, 65.95, 65.89; H, 10.12, 10.80, 10.57.

Method II. This experiment differed from Method I only in the solvent used. In this case, 80 ml. of dry benzene and 80 ml. of dry toluene were used. The product was distilled; it boiled at 100-101°/0.3 mm. The yield was 6 g. (13.5 percent of the theoretical quantity).

Method III. Again Method I was modified only in respect to quantities of solvent. In this run 80 ml. dry toluene and 60 ml. of dry benzene were used. Six grams of product was again obtained. The product was distilled; it boiled at 114-115°/1.3 mm.

Method IV. A 500-ml., three-necked flask was fitted with reflux condenser, stirrer, and dropping funnel. To the flask was added 6.1 g. (0.25 atom) of magnesium turnings and the apparatus was flamed while a slow stream of dry air was drawn through it. The flask was cooled to room temperature and 200 ml. of absolute ether was added. A solution of 43 g. (0.22 mole)

of N,N-diethylbromoacetamide and 21.2 g. (0.25 mole) of cyclopentanone in 200 ml. absolute ether was prepared. Fifty ml. of this solution and one ml. of methyl iodide was added to the flask. Stirring was started and the reaction commenced after a few minutes. The rest of the solution was added dropwise at such a rate that the reaction boiled gently. Toward the end of the addition it was necessary to heat the flask. The reaction mixture was heated under reflux for one hour after all the reactants have been added. A thick semi-solid mass formed which was dissolved in 200 ml. of ten percent sulfuric acid solution. The ethereal solution was washed with five percent sodium carbonate solution and finally with water until neutral, and was then dried over magnesium sulfate. The drying agent was removed by filtration. A small amount of a black viscous oil remained after the ether had been removed by distillation.

This tar was not identified.

Preparation of N,N-Diethyl-1-hydroxycyclohexaneacetamide.

The condensation of 35 g. (0.18 mole) of N,N-diethylbromoacetamide and 19.6 g. (0.2 mole) of freshly distilled cyclohexanone in a solution of 80 ml. dry benzene and 80 ml. dry toluene was effected by the use of 14.3 g. (0.2 atom) of zinc-copper alloy. It was necessary to use vigorous stirring^{1*} to obtain the maximum yield. The reaction mixture was treated in the usual manner. The product was distilled; it boiled at 94-95^o/0.2 mm.

¹This ketone was obtained from E. I. DuPont De Nemours.

** In all the experiments using cyclohexanones vigorous stirring was necessary to prevent the insoluble zinc complex from adhering to the zinc and hindering the reaction.

The yield of slightly yellow amide was 23 g. (60 percent of the theoretical amount).

A portion was purified by distillation and was analyzed. The index of refraction and density were determined and the molar refraction calculated. D_{25}^{25} , 1.005; n_D^{25} , 1.4787;

$M_r(\text{obs.})$: 60.07; $M_r(\text{cal.})$: 60.90.

Anal. Calc'd. for $C_{12}H_{23}NO_2$: C, 67.70; H, 10.80; N, 6.42.

Found: C, 66.86, 66.61, 66.84, 66.94; H, 10.72, 10.87, 10.40, 10.55; N, 6.60, 6.53.

Preparation of N,N-Diisopropyl-1-hydroxycyclohexanecetamide. A solution of 49 g. (0.22 mole) of N,N-diisopropylbromacetamide and 24.5 g. (0.25 mole) of cyclohexanone in 100 ml. of toluene and 25 ml. of benzene was prepared. The condensation was carried out in the usual manner by means of 18 g. (0.25 atom) of zinc-copper alloy. The product was distilled; it boiled at 102-103°/0.2 mm. The yield was 22 g. (42 percent of the theoretical amount).

A portion was redistilled for analysis. This fraction was distilled at 106°/0.4 mm. n_D^{24} , 1.4774.

Anal. Calc'd. for $C_{13}H_{27}NO_2$: C, 69.71; H, 11.22. Found: C, 69.48, 69.43; H, 10.84, 10.86.

Preparation of N,N-Diethyl-1-hydroxy- α -methylcyclohexanecetamide.

Method I. A solution of 19.6 g. (0.2 mole) of cyclohexanone and 37.5 g. (0.18 mole) of N,N-diethyl- α -bromopropionamide in 80 ml. of dry benzene and 80 ml. of dry toluene was prepared and the reaction was carried out using 14.3 g. (0.20 atom) of zinc-copper alloy by the usual procedure. The product was

distilled, it boiled at 108-109°/0.1 mm. The yield was 8 g. (14.5 percent of the calculated quantity).

A portion was purified and a fraction which distilled at 108-109°/0.1 mm. was analyzed. The density and refractive index were determined and the molar refraction calculated. D_{25}^{25} , 0.9978; n_D^{25} , 1.4795; M_r (obs.), 64.65; M_r (cal.), 65.21. Anal. Calc'd. for $C_{13}H_{25}NO_2$: C, 68.72; H, 11.02. Found: C, 68.64, 68.40; H, 11.21, 10.60.

Method II. The procedure used in Method I was repeated using 40 ml. of dry benzene and 120 ml. of dry toluene for the solvent. The product was distilled; it boiled at 108-109°/0.1 mm. and had a refractive index of 1.4788 at 26°. The yield was 12 g. (30 percent of the theoretical quantity).

Method III. This experiment duplicated the first method except that 160 ml. of dry toluene was used as the solvent. The product was distilled; it boiled at 108-109°/0.1 mm. and had a refractive index of 1.4797 at 26°. The yield was 7.5 g. (18 percent of the theoretical amount).

Preparation of N,N-Diethyl-1-hydroxy-4-methylcyclohexane-acetamide.

Method I. This condensation was carried out in the usual manner with 14.3 g. (0.2 atom) of zinc-copper alloy as condensing agent. The reactants were 24.4 g. (0.2 mole) of 4-methylcyclohexanone* and 35 g. (0.18 mole) of N,N-diethyl-

*This ketone was Eastman Kodak's white Label grade. It was used without further purification.

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bromoacetamide in 80 ml. of dry benzene and 80 ml. of dry toluene. The product was distilled; it boiled at 104-105°/0.3 mm. The yield was 24 g. (59 percent of the theoretical quantity).

A portion was purified and a fraction which distilled at 104-105°/0.3 mm. was analyzed. The molar refraction was determined from the density and refractive index. n_{25}^{25} , 0.9872; n_D^{25} , 1.4760; $M_r(\text{obs.})$, 64.87; $M_r(\text{cal.})$, 65.51.
 Anal: Calc'd. for $C_{13}H_{25}NO_2$: C, 68.72; H, 11.02. Found: C, 68.23, 68.43; H, 10.83, 11.11.

Method II. A solution of 33 g. (0.22 mole) of N,N-diethylchloroacetamide and 26 g. (0.25 mole) of 4-acetylcyclohexanone in 100 ml. of dry toluene and 25 ml. of dry benzene was prepared. This solution was treated with 18 g. of zinc-copper alloy in the usual manner. The product was distilled; it boiled at 114-115°/0.4 mm. and had a refractive index of 1.4470 at 25°. The yield was 16 g. (32 percent of the calculated quantity).

Attempted condensation of Acetophenone with α -bromoacetanilide. A 500-ml. three-necked flask was fitted with a reflux condenser and a stirrer. A crystal of iodine and 14.3 g. (0.2 atom) of zinc-copper alloy were added and the flask was placed with a luminous flame while a slow stream of dry air was drawn through it.

A mixture of 39 g. (0.18 mole) of α -bromoacetanilide and 24 g. (0.2 mole) of acetophenone* in 200 ml. of dry benzene and

*The acetophenone was obtained from the Paragon Testing Laboratory. This ketone was purified by distillation; it boiled at 88-89°/15 mm.

100 ml. of dry toluene was prepared and the solution was heated to cause the solid to dissolve. The hot solution was added to the reaction in 25-ml. portions. After all the reagents had been added, the reaction mixture was refluxed for one hour and then worked up in the usual manner. After most of the solvent had been removed, petroleum ether (60-80°) was added until a slight turbidity was noted. On cooling, a yellow powder precipitated and was collected on a filter. The very impure material weighed 25 g. and had a melting range of 80-100°. After three recrystallizations the material melted at 112-115°. A mixed melting point with pure acetanilide gave no depression. In the light of the results of a similar experiment with α -bromoacetanilide and 2-ethylhexaldehyde this material was thought to be acetanilide and no further work was done.

Preparation of N,N-Diethyl- β,β -diphenylhydraerylamide.

A solution of 43 g. (0.22 mole) of N,N-diethylbromacetamide and 46.5 g. (0.25 mole) of benzophenone* in 150 ml. of dry toluene and 40 ml. of dry benzene was prepared. The solution was treated in the usual manner with 18 g. (0.2 atom) of zinc-copper alloy. When the reaction was complete, enough benzene was added to dissolve the white powder that had formed during the process. The zinc complex was then decomposed and washed by the standard method. A crystalline residue remained after

*The benzophenone was the product of the Eastman Kodak Co. The material was purified by distillation; the ketone used boiled at 177-178°/20 mm.

the solvent had been removed by distillation. This solid crystallized from 300 ml. of petroleum ether (60-80°) in large, chunky, grayish-white crystals that melted at 89-90° (uncorr.). The yield was 35 g. (53 percent of the calculated quantity).

An analytical sample recrystallized until a constant melting point of 92.6-93.6° was obtained.

anal. Calc'd. for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.75. Found: C, 77.00, 76.96; H, 8.01, 8.12.

General Experiments

Preparation of N,N-Diethyl- β -phenyleinnamide. This material was made by the dehydration of N,N-diethyl- β , β -diphenylhydracrylamide by a method similar to that of Bachmann and Edgerton (3).

Three grams of N,N-diethyl- β , β -diphenylhydracrylamide was heated on a steam bath for fifteen minutes with 20 ml. of 99 percent formic acid. The cooled reaction mixture was poured into 50 ml. of water and the resulting mixture was extracted with three, ten-ml. portions of benzene. The benzene extracts were combined and washed with five percent potassium carbonate solution and with water until the organic layer was neutral. The benzene solution was dried over magnesium sulfate and the solvent was removed by distillation. The solid residue crystallized from petroleum ether (60-80°) in white needles that melted at 84-87° (uncorr.). The yield was 2.5 g. (90 percent of the calculated amount).

The substance was purified for analysis by recrystallization; the purified material melted at 83.6-84.3°.

Anal. Calc'd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53. Found: C, 81.87, 81.99; H, 7.46, 7.47.

Preparation of α,β -dibromo-N,N-diethyl- β -anisylacrylamide. One gram of N,N-diethyl- β -anisylacrylamide was dissolved in 10 ml. of carbon tetrachloride and a 5 percent solution of bromine in carbon tetrachloride was added until the color of the bromine was no longer discharged. The carbon tetrachloride was removed by heating the solution on a steam bath and the residue was recrystallized from a 1:1 mixture of benzene and petroleum ether (60-80°). The product was white needle-like crystals which melted at 120-121° (uncorr.). The yield was 1.5 g. (88 percent of the calculated amount).

An analytical sample was prepared by recrystallization, the purified material melted at 122-122.8°. It is necessary to heat the bath to about 115° before inserting the melting point capillary to obtain reproducible melting points.

Anal. Calc'd. for $C_{14}H_{19}Br_2NO_2$: C, 42.75; H, 4.84. Found: C, 43.16, 42.86; H, 5.03, 5.23.

Preparation of α,β -Dibromo-N,N-diisopropyl- β -anisylacrylamide. One gram of N,N-diisopropyl- β -anisylacrylamide was dissolved in ten ml. of carbon tetrachloride; the resulting solution was treated with a five percent solution of bromine in carbon tetrachloride until the color of the bromine was no longer discharged. The carbon tetrachloride was evaporated on a steam bath and the residue was recrystallized from petroleum ether (60-80°). The white needles melted at 132-134 (uncorr.). The yield was 1.5 g. (93 percent of the calculated amount).

An analytical sample melted at 139-140°.

Anal. Calc'd. for $C_{16}H_{23}Br_2NO_2$: Br, 38.01. Found: Br, 37.70, 38.05.

Attempted Dehydration of N-ethyl-(3-hydroxy-5-phenyl-4-penten)anilide. Three grams of N-ethyl-(3-hydroxy-5-phenyl-4-penten)anilide was heated for fifteen minutes on a steam bath with 20 ml. of 99 percent formic acid. The resulting solution was cooled to room temperature and poured into 50 ml. of water. The water suspension was extracted with three portions of ether and the ethereal solution was washed with five percent potassium carbonate solution and with water until the organic layer was neutral. Attempts to recrystallize the product met with failure.

The oil was dissolved in carbon tetrachloride and treated with bromine in carbon tetrachloride. The solvent was removed but this product did not crystallize.

Preparation of Zinc-copper Alloy. A clay crucible was charged with 2760 g. of C. P. zinc shot and heated in an electric furnace until the zinc fused. Two hundred forty grams of pure copper shot was then stirred into the molten mass until a homogenous solution resulted. The molten mass was then poured into a mold containing an axially located steel bar so that a bar of alloy containing a centered steel rod extending from one end was formed.

The alloy was turned on a lathe and the turnings cleaned in a Soxhlet extractor with a 1:1 mixture of benzene and

petroleum ether (60-80°). The alloy was dried and used without further purification.

SUMMARY

1. The substitution of N,N-disubstituted- α -haloamides for α -haloesters in the Reformatsky reaction has been studied and shown to be practical.
2. Amides and N-monosubstituted amides did not yield the desired products.
3. Ten N,N-disubstituted- α -haloamides, nine ketones, and five aldehydes gave sixteen different hydroxy amides. Anis- aldehyde with two different α -haloamides yielded an unsaturated product.
4. Furfural and phenylacetaldehyde did not react in the expected manner.
5. It has been shown that yields of product are somewhat lower when α -bromoamides are substituted for corresponding α -bromoesters in the Reformatsky reaction.

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