observations show that its melting point in vacuum does not differ greatly from that in air.

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, NEW YORK   RECEIVED FEBRUARY 23, 1939

Study of the Reformatsky Reaction; Efficient Procedure for the Preparation of Bromoacetic Ester in Large Quantities

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

In the preparation of intermediates in certain synthetic studies, it was found necessary to prepare large quantities of the esters of dihydro- and tetrahydrophenylacetic acid. It was decided to proceed by means of the Reformatsky reaction.[1]

The procedures reported in the literature were repeated carefully. However, the yields were found to be poor and not suitable for the preparation of large quantities. A systematic study of the individual factors influencing the reaction was, therefore, initiated. Temperature, solvents, form of zinc or magnesium and methods of dehydration of the condensation product were studied. A procedure was developed wherein the reaction proceeds smoothly and gives good yields by controlling a few simple conditions.

The optimum temperature of the reaction mixture was found to be between 90–105°. At this temperature the reaction proceeds at a rapid rate, but not so rapidly as to become uncontrollable. The use of benzene alone as a solvent is not advisable except when the concentration of reactants is such as to raise the boiling point of the mixture to the required temperature. Numerous authors have employed conditions where a low boiling solvent or no solvent at all was used, but on checking their conditions we found that in the cases where the best yields were obtained the concentration of reactants was such as to give a temperature within the desirable range. A simple way of achieving and maintaining the desired temperature is to use as solvent, approximately a 1:1 mixture of benzene and toluene.

For best yield, smoothness of reaction, rapidity and convenience zinc is preferable to magnesium. The zinc used in the reaction should be in the form of zinc foil. This must be carefully scraped with sandpaper to cut through any impurities which may cover it. Cleaning the zinc by means of alkali is not recommended. The use of mossy zinc was found to be unsatisfactory, for it is not of

uniform thickness, difficult to clean and consequently uncertain in its reaction. Powdered zinc is not recommended for it is difficult to clean and hence occasionally the reaction is slow in starting. Once the reaction is started, it often becomes quite violent and is difficult to control. Copper–zinc couples have practically no advantage over zinc foil in our experience.

After the condensation product has been formed, and the zinc salt is hydrolyzed, it is sometimes a problem to dehydrate the resulting product. After trying numerous reagents such as potassium bisulfate, phosphorus pentoxide in various solvents, zinc chloride and sulfuric acid,[2] it was observed that the best method for obtaining good yields without decomposition is by the use of dry hydrogen chloride, hot or cold. The dehydration is usually quantitative. Numerous β-hydroxy esters can be dehydrated in this manner. Typical examples are the compounds obtained from the action of bromoacetic esters on cyclohexanones, the 1, 2 and 3-methylcyclohexanones, ethyl methyl ketone, methyl butyl ketone and 3,7-dimethyloctanal-1. In the terpene series a few cases were encountered where the dry hydrogen chloride polymerized the resultant product and was therefore of no use. In some cases, of course, it is not necessary to dehydrate the product formed, splitting out of water being spontaneous. An example of this type was encountered with the condensation of bromoacetic ester with methylcyclohexenone to form dihydroethylphenylacetate.[3]

An example of the recommended procedure is given below. These conditions have been applied by the authors and co-workers with consistent results to numerous aldehydes and ketones of various types. The yields rarely fall below 60% and are usually about 70%.
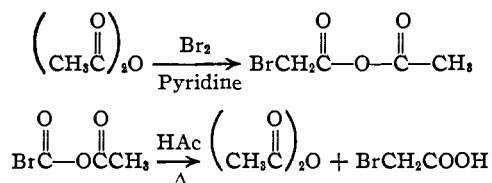
During these studies the authors had occasion to use large amounts of bromoacetic ester. A rapid and economical laboratory method for producing this compound in good yields was devised and is described herein. Acetic anhydride with pyridine makes an efficient catalyst for smooth bromination.

If the halogen carrier, pyridine, is omitted the bromination will take place, but the reaction here is from two to three times as long. Acetic an-

(1) Wallach, *Ann.*, **343**, 287 (1905); **365**, 261 (1909).

(2) Wallach and Salkind. *Ann.*, **314**, 153 (1901); Tetry, *Bull. soc. chim.*, [3], **27**, 600 (1902); DeFazi, *Gazz. chim. ital.*, [1], **45**, 555 (1915).

(3) Wallach, *Ann.*, **323**, 138 (1902).

hydride itself is readily brominated in the presence of pyridine. If glacial acetic acid is added subsequently and the reaction mixture is boiled, acetic anhydride is regenerated, liberating bromoacetic acid. The two products can then be separated by distillation. These observations would indicate that the reaction probably proceeds as follows:

$$\left(CH_3\overset{\overset{O}{\|}}{C}\right)_2O \xrightarrow[\text{Pyridine}]{Br_2} BrCH_2\overset{\overset{O}{\|}}{C}—O—\overset{\overset{O}{\|}}{C}—CH_3$$

$$Br\overset{\overset{O}{\|}}{C}—O\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[\Delta]{HAc} \left(CH_3\overset{\overset{O}{\|}}{C}\right)_2O + BrCH_2COOH$$

Experimental

Bromoacetic Acid Ester.—The reaction is carried out in a hood. An all-glass outfit is advisable. If not available, one-hole asbestos stoppers may be made by soaking strips of asbestos in water, wrapping them around pieces of glass tubing of slightly less than the desired diameter, to the desired outer diameter, and allowing them to dry at 110°. A mixture of 1000 cc. of glacial acetic acid, 200 cc. of acetic anhydride and 1 cc. of pyridine is added to a 5-liter three-necked flask fitted with reflux condenser, drying tube and dropping funnel. The mixture is heated to boiling, the flame is removed and 1100 g. of bromine is dropped in at a rate designed to keep the mixture just refluxing. At the beginning there is a lag (ten minutes) before the reaction starts. The mixture clears up and decolorizes the bromine as rapidly as it is added. Toward the end the reaction slows up and the solution remains colored. Heat is then applied and the reaction mixture is refluxed until decolorized (one hour). The excess acetic anhydride and glacial acetic acid are now removed under slight vacuum (about 300 cc. recovered), 2 liters of 95% ethyl alcohol and 200 cc. of concentrated sulfuric acid (less may be used if absolute alcohol is used) is added to the residue. The mixture is refluxed for two hours and then poured into four liters of water. The bromoacetic ester is separated, dried over sodium sulfate and distilled: b. p. 159°; yield 785 g. of product boiling within 0.5°.

Reformatsky Reaction.—A mixture of 800 cc. of benzene and 700 cc. of toluene is made with 334 g. (2 moles) of bromoacetic ester and (2 moles) of the required ketone. Three hundred cc. of this mixture is added to a five-liter three-necked flask fitted with mechanical stirrer, condenser with drying tube and dropping funnel; 130 g. (2 moles) of zinc foil which has been scraped with sandpaper is cut up in strips and added to the flask. A few crystals of iodine are added and the stirrer is started. The mixture is heated by means of a boiling water-bath. A vigorous reaction sets in. The remainder of the reaction mixture is now added through the dropping funnel at a rate designed to keep the mixture refluxing but not too vigorously. After the addition is complete, stirring is continued for two hours more. Practically all the zinc dissolves. The mixture is cooled. The condensation product is decomposed with dilute sulfuric acid (sufficient to dissolve

all the zinc hydroxide). The benzene–toluene layer is separated, dried over sodium sulfate and vacuum distilled on a water-bath to remove the benzene and toluene. Through the residue heated on a boiling water-bath is passed dry hydrogen chloride for two hours. The material is vacuum distilled. The water which has split out comes over first and then the unsaturated ester; yield 60–70%. For tetrahydrophenylethyl acetate the yield is 238 g. (about 71%).

PEDIATRIC RESEARCH LABORATORY
JEWISH HOSPITAL OF BROOKLYN
BROOKLYN, NEW YORK   RECEIVED JANUARY 21, 1939

### Dehydration of Hydroxy Compounds by Pyrolysis of their Potassium Sulfate Esters; Cholesterilene and Camphene

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

While carrying out investigations on methods for the isolation of sterols from natural occurring sources,[1] it was observed that if anhydrous potassium cholesteryl sulfate is heated at 100° for an hour in a sealed tube or autoclave, complete decomposition takes place with the separation of a colorless oil which crystallizes on cooling. The crystals were readily identified as cholesterilene (3,5-cholestadiene), the yield being excellent. Potassium acid sulfate was split out yielding the unsaturated compound.

$$\overset{\overset{H}{|}}{-C}-\overset{|}{C}OSO_3K \xrightarrow{\Delta} \rangle C=C\langle + KHSO_4$$
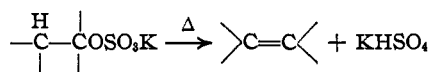
Since a method for preparing potassium cholesteryl sulfate in quantitative yields is described herein, this is by far the best method for preparing large amounts of cholesterilene.[2]

If water is present, the reaction takes another route, cholesterol being regenerated. This hydrolysis is catalyzed by small amounts of hydrogen ion.

$$ROSO_3K \xrightarrow[\text{HOH}]{\Delta} ROH + KHSO_4$$
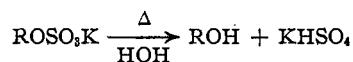
The ease with which the unsaturated compound is formed, encouraged us in the hope that this method might be applied as a general method for the dehydration of compounds where there existed danger of rearrangement. Potassium bornyl sulfate was therefore chosen as a test compound. It is well known that dehydration of borneol yields a variety of dehydration products and

(1) Natelson and Sobel, J. Biol. Chem., 109, 687 (1935); Natelson, Sobel and Kramer, ibid., 105, 763 (1934).

(2) Haltori, THIS JOURNAL, 60, 3082 (1938); Bergmann, J. Org. Chem., 1, 567 (1937).