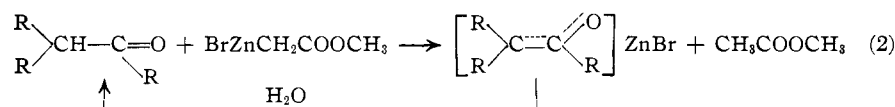# Enolization in the Reformatsky Reaction

BY MELVIN S. NEWMAN

In the Reformatsky reaction it is generally thought that zinc reacts with a bromoester to form an organozinc intermediate which then adds to the ketone or aldehyde to yield a bromozinc derivative of a β-hydroxyester, as follows

$$\begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} CH-C \begin{array}{c} \diagup O \\ \diagdown R \end{array} + BrZnCH_2COOCH_3 \longrightarrow$$

$$\begin{array}{c} \qquad\qquad OZnBr \\ R \qquad\qquad | \\ \diagdown \\ \diagup CH-C-CH_2COOCH_3 \quad (1) \\ R \qquad\qquad | \\ \qquad\qquad R \end{array}$$
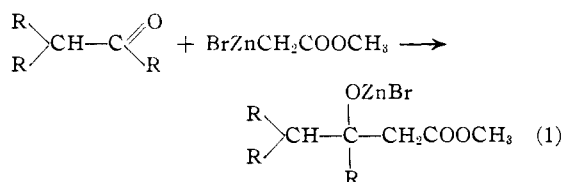
The recovery of ketone from the products of such a reaction would seem to indicate incomplete reaction. However, it was found to be a fact that practically all of the theoretical amount of zinc was consumed in experiments where considerable amounts of ketone were recovered. This finding suggested that the ketone reacted in some way with the organozinc intermediate so that on hydrolysis the ketone was regenerated. Bearing in mind the probability that the Reformatsky reaction involves an organozinc intermediate which would be expected to behave like other organometallic compounds, it seemed likely that the recovered ketone was tied up as an enolate during the reaction,[1] as follows

$$\begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} CH-C=O + BrZnCH_2COOCH_3 \longrightarrow \left[\begin{array}{c} R \\ \diagdown \\ \diagup \\ R \end{array} C \vdots\vdots C \begin{array}{c} \diagup O \\ \diagdown R \end{array} \right] ZnBr + CH_3COOCH_3 \quad (2)$$

Acetomesitylene was chosen as an excellent test for this hypothesis because it has been shown to react by the enolization mechanism with Grignard reagents[2] and with organolithium[3] and organosodium[3] compounds. It was found that acetomesitylene reacted vigorously with zinc and methyl bromoacetate. After hydrolysis of the reaction mixture 90% of acetomesitylene was recovered and in addition approximately 50% of the theoretical amount of methyl acetate was isolated.

When 23.3 g. of acetomesitylene, 23.0 g. of methyl bromoacetate and 5 g. of freshly sandpapered zinc foil[4] were brought together in 100 cc. of dry sulfur-free benzene, an extremely vigorous reaction ensued. Approximately the theoretical amount of zinc was consumed in a short time. After hydrolysis with dilute hydrochloric acid the benzene layer was distilled. On fractionation of the low boiling fraction, 5.3 g. (50%) of methyl acetate was obtained. This was identified by boiling point, 57–58° uncor., odor and hydrolysis to yield acetic acid, identified as its p-bromophenacyl ester[5], m. p. and mixed m. p. 83–84° cor. More methyl acetate was present as judged by the boiling point and odor of intermediate fractions. From the higher boiling fraction there was isolated 20.9 g. (90%) of acetomesitylene, b. p. 124–125° uncor., at 20–21 mm. This was identified further by conversion in 64% yield to 3,5-dinitro-2,4,6-trimethylacetophenone,[6] m. p. and mixed m. p. 139–140° cor.

In a similar experiment it was shown that methyl acetate could be distilled from the reaction mixture before hydrolysis, thereby proving that the methyl acetate formed did not arise from a reaction of any bromozinc intermediate with water. It should be emphasized that the formation of methyl acetate in a Reformatsky reaction is entirely analogous to the formation of methane in a Zerewitinoff determination. In order to rule out the possibility that the methyl acetate might have arisen from some other side reaction, zinc and methyl bromoacetate were refluxed in benzene for a day. Considerable reaction occurred but at no time was a positive organometallic color test with Michler ketone[7] obtained. A small amount of methyl acetate was produced but not nearly enough to account for the methyl acetate resulting when acetomesitylene was present. Therefore, on the basis of the above facts, it is concluded that in the Reformatsky reaction acetomesitylene reacts mainly by the enolization mechanism.

(1) Newman, THIS JOURNAL, **62**, 870 (1940).

(2) Kohler and Baltzly, *ibid.*, **54**, 4015 (1932).

(3) Gilman and Jones, *ibid.*, **63**, 1162 (1941). In this paper it is pointed out that enolization of a ketone prior to reaction with an organometallic compound does not necessarily have to occur. It may be that the initially formed complex between the carbonyl oxygen and the organometallic reagent react so that the products characteristic of an enolization reaction are formed. See also Arnold, Bank and Liggett, *ibid.*, **63**, 3444 (1941).

(4) Natelson and Gottfried, *ibid.*, **61**, 970 (1939). The zinc foil was obtained from the J. T. Baker Co., Phillipsburg, N. J.

(5) Judefind and Reid, *ibid.*, **42**, 1043 (1920).

(6) Fuson and Walker, *ibid.*, **52**, 3269 (1930). Under the same conditions the pure known compound yielded 66% of the derivative.

(7) Gilman and Schulze, *ibid.*, **47**, 2002 (1925). To allow for the possibly lesser reactivity of an organozinc compound, the test solution was heated for one to five hours before hydrolysis, at the suggestion of the Referee. However, the success or failure in obtaining a color test does not affect the argument in favor of enolization, for no appreciable amount of methyl acetate is formed unless acetomesitylene is added.

A solution of 67.5 g. of methyl bromoacetate in 350 cc. of dry sulfur-free benzene and a few crystals of iodine was refluxed over 32 g. of zinc[4] for twenty hours. Shortly after the refluxing commenced the solution turned yellow-green. A test[7] with Michler ketone at this stage was negative. After about thirty minutes of refluxing an orange-yellow viscous complex was seen to adhere to the active spots on the zinc. Some of this complex was removed on a glass rod when it first appeared, but this also gave a negative color test. After twenty hours of refluxing the decanted solution was distilled through a 10–15 plate column. With a reflux ratio of over 80 to 1 about 3 g. of a fraction, b. p. 57–64°, was collected. Methyl acetate was present in this as judged by boiling point, odor, and identification of acetic acid on hydrolysis as the p-bromophenacyl ester.[5] On weighing the zinc it was found that 19.5 g. had reacted. This amounts to 68% of that required to react with the bromoester used.

The isolation of ketone from the products of Reformatsky reactions does not necessarily mean that the ketone was tied up as an enolate during the reaction, but, if the theoretical amount of zinc was consumed in a short time during the reaction and if no insoluble complex coated out on the zinc to hinder complete reaction, it seems most likely that enolization offers the best explanation for the recovery of unchanged ketone. In the past few years the author has carried out many such reactions in which, although ample excesses of zinc and bromoesters were present, and approximately the theoretical quantity of zinc was rapidly consumed, considerable amounts of starting ketone were recovered. At the time when most of these reactions were run, the possibility of enolization as a factor in Reformatsky reactions was not under consideration. Accordingly, a thorough study of the factors which influence the enolization of ketones in this reaction cannot be reported. However, it is possible to point out a few observations which seem to be substantiated by the experimental results.

The ketones studied were 1-keto-2-phenyl-1,2,-3,4-tetrahydronaphthalene,[1] I, 1-keto-2-o-tolyl-3-methyl-1,2,3,4-tetrahydronaphthalene,[8] II, and 4-keto-1,2,3,4-tetrahydrophenanthrene,[9] III.

Preparation of Ketone

Ketones I and II were prepared as previously reported. Ketone III was prepared as follows. The acid chloride prepared in benzene solution from 199 g. of γ-2-naphthylbutyric acid and phosphorus pentachloride was dissolved in 500 cc. of sulfur-free dry benzene, and 127 g. of aluminum chloride[10] was added in portions with stirring. Very

(8) Newman, THIS JOURNAL, **62**, 2295 (1940).

(9) Compare Haworth, J. Chem. Soc., 1125 (1932), and Bachmann and Edgerton, THIS JOURNAL, **62**, 2219 (1940).

(10) Calco Chemical Co., Standard grade, anhydrous.

little hydrogen chloride was evolved and the color of the complex first formed was still a pale yellow-green when 90% of the aluminum chloride had been added. Also there had been considerable evolution of heat. When the last portions of aluminum chloride were added the color deepened rapidly to a red-brown, the temperature started to rise rapidly (cooling required), and much hydrogen chloride was evolved. After regulation of the internal temperature at 35–40° for one hour, the temperature was raised to 60° for an hour and to 65° for one-half hour. The mixture was then cooled and worked up in the usual manner. On rapid vacuum distillation at 2 mm. a pale yellow viscous oil, 170 g. (93%), was obtained. By crystallization from 400 cc. of alcohol, two crops of crystals totalling 157 g. (86%), m. p. 66.0–67.4° cor., were obtained. About 3 to 5% of starting acid was recovered from alkaline extracts of the reaction mixture.

General Description of Procedure

A solution of the pure ketone (usually 0.1 to 0.2 mole) and bromoester (in 15–20% excess) in dry sulfur-free benzene (80–100 cc. per 0.1 mole) was placed in a round-bottom flask fitted to a ground-in condenser which could be changed from refluxing to distilling by turning a stopcock. This solution was distilled for a short while to render completely anhydrous. An excess of freshly sandpapered zinc foil was added while the solution was still hot, and, when desired, a few crystals of iodine were allowed to fall on the foil. In most cases a vigorous exothermic reaction set in as soon as the solution was heated to boiling. Refluxing then continued spontaneously until the reaction was virtually complete. This took about ten to twenty minutes. After further refluxing with added heat for not more than thirty minutes the reaction mixture was cooled and decomposed with dilute hydrochloric acid. The organic material was separated by ether extraction and the unreacted zinc collected and weighed.[11] After thorough washing with dilute acid and water, the solvent was removed from the benzene layer and the residue was heated for a short while in the neighborhood of 200° to effect dehydration. When iodine was used in starting the reaction it was generally unnecessary to add more iodine for dehydration. The residue was vacuum distilled, the distillate refluxed with dilute aqueous–alcoholic potassium hydroxide, and the hydrolyzate separated into acidic and neutral fractions. The original ketone was recovered from the neutral fraction by vacuum distillation, crystallization, or a combination of the two, and the yields of ketone reported represent practically pure ketone. The acid fractions were crystallized from benzene. In some cases all of the acid crystallized. The amounts of noncrystalline acid were determined by evaporating the solvent from the mother liquors to constant weight of residue, and these values were checked by esterification and vacuum distillation of the ester.

Discussion of Results

From a consideration of the experiments cited

(11) If dilute hydrochloric acid is used, it is possible to separate the zinc rapidly before any appreciable amount of it reacts with the acid. It is surprising how slowly the unreacted zinc is attacked by dilute acids. Washing with acetone hastens the cleaning of the zinc prior to drying and weighing.

below the following conclusions seem justified.[12]

1. The use of a small amount of iodine to initiate the reaction decreases enolization.[13] In two experiments with ketone I and ethyl α-bromopropionate, 38% of acid[14] and 27% of ketone I were obtained when iodine was used. Without iodine the yields were 23% of acid[14] and 42% of ketone. In other experiments with ketone III and ethyl bromoacetate, when iodine was used 87% of acid and 6% of ketone III were isolated. Without iodine the yields were 77% of acid and 17% of ketone.

2. The use of dioxane as a solvent promotes enolization. In experiments with ketone I and ethyl bromoacetate, 68% of acid[14] and a small but undetermined amount of ketone were obtained in benzene as solvent. In pure dioxane the reaction took place more vigorously than in benzene but the yields were 29% of acid[14] and a large but undetermined amount of ketone I. No iodine was used. In other experiments with methyl bromoacetate and ketone II, when iodine was

used in benzene, 52% of acid and 41% of ketone II were isolated. In dioxane and with no iodine the reaction was much more vigorous than in benzene but only 10% of acid and 70% of ketone were obtained.

3. The tendency to cause ketones to react by enolization increases in the following esters: ethyl bromoacetate <ethyl α-bromopropionate <ethyl α-bromobutyrate. In experiments with ketone I using no iodine, ethyl bromoacetate yielded 68% of acid[14] and a small amount of ketone, whereas ethyl α-bromopropionate yielded 23% of acid and 42% of ketone. In experiments with ketone I using iodine, ethyl α-bromopropionate yielded 38% of acid[14] and 27% of ketone I, whereas ethyl α-bromobutyrate yielded 28% of acid[14] and 48% of ketone I. In experiments with ketone III using no iodine, ethyl bromoacetate yielded 77% of acid and 17% of ketone III, whereas ethyl α-bromopropionate yielded 55% of acid and 39% of ketone III.

(12) It should be emphasized that the experiments cited were not isolated cases but those in which the results had been duplicated to within a few per cent. In all of these cases the zinc reacted approached the theoretical and in all cases the reactions had proceeded for a maximum of ninety minutes.

(13) The amount of enolization is probably more accurately estimated by the amount of ketone recovered than by the amount of acid isolated. Those cases where the total amount of products accounted for is less than 85% were from earlier work, where the technique was not as good as in later work.

(14) The percentages indicated in these cases represent pure crystalline acid only; additional non-crystalline acid was present but was not accounted for.

Summary

Evidence is presented that the recovery of starting ketone from the products of a Reformatsky reaction may be due to enolization of the ketone during reaction. In the case of acetomesitylene, 90% of the ketone is recovered after reaction. A few factors influencing the enolization of ketones in the Reformatsky reaction are discussed.

Investigation of Pyrazole Compounds. I. The Reaction Product of Phenylhydrazine and Ethyl Cyanoacetate

BY A. WEISSBERGER AND H. D. PORTER

Conrad and Zart[1] treated ethyl cyanoacetate with phenylhydrazine, using sodium alcoholate as a condensing agent, and obtained a colorless compound of the composition $C_9H_9N_3O$ and the m. p. 219°. This, they assumed to be 1-phenyl-3-hydroxy-5-pyrazolone-imide, I. However, the reaction between ethyl cyanoacetate and phenylhydrazine could also lead to the isomeric 1-phenyl-3-amino-5-pyrazolone, II. The intermediate in the formation of I might be the β-cyanoacetylphenylhydrazine, III, while the formation of

β-imino-β-(β-phenylhydrazino)-propionic ester, IV, as the primary product would lead to II.

The compound synthesized by Conrad and Zart is of importance in color photography,[2] and it appeared desirable to get definite information about its structure. In order to decide between I and II, I was synthesized in an unambiguous way, starting with 1-phenyl-3-carbethoxy-5-pyrazolone, V.[3] This compound can be prepared by ring closure from the well-characterized ethyl

(1) Conrad and Zart, *Ber.*, **39**, 2282 (1906).

(2) British Patent 478,990.

(3) Wislicenus, *Ann.*, **246**, 319 (1888).