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ASYMMETRIC SYNTHESIS IN A REFORMATZKY REACTION PREPARATION OF OPTICALLY ACTIVE β-HYDROXY ACIDS

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SUMMARY

Reaction of benzaldehyde with optically active bromoacetic ester derivative I in a Reformatzky reaction gives, after hydrolysis of the resulting ester, laevorotatory B–hydroxy–Bphenyl phenyl-propionic acid. Moreover, reaction of ethyl bromoacetate with acetophenone in the presence of zinc and 1,2:5,6-di-O-isopropylideno-α-D-glucofuranose (II) is accompanied by partial asymmetric synthesis as is shown by hydrolysis of the resulting ester to laevorotatory B-hydroxy -B-phenylbutyric acid.

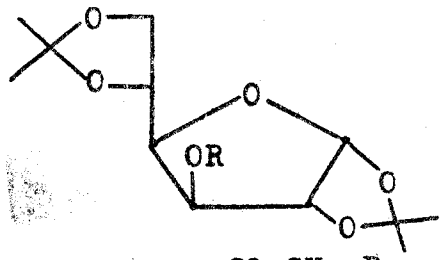
INTRODUCTION

The older chemical literature concerned with the Reformatzky reaction has been reviewed[1] from a preparative standpoint but without regard to stereochemistry. In a formal sense, the Reformatzky reaction may be compared with the Grignard reaction in which the organozinc reagent prepared from an α–haloester replaces the Grignard reagent. In both reactions a new chiral center is created if the alkyl groups of the ketone and reagent are different. Although, the Grignard and Reformatzmatzky reactions appear to be similar in a formal sense, the Grignard rea-reagent has a true metallic bond, while the Reformatzky reagent is best represented as an enolate ion or as a complex in which the halogen and zinc atoms are held in a cyclic structure. It is commonly accepted[2] that in Reformatzky reaction an organozinc intermediate analogous to Grignard reagent is first formed and this subsequently reacts with carbonyl compounds, thus, it seems that a partial asymmetric reaction may occure during the addition of an organometalic compound to a

carbonyl group, when it is the organometallic compound which contains a fixed center of asymmetry. Before this observation the only successful examples of an asymmetric reaction occuring during the addition of an organometallic compound to a carbonyl group had been when the fixed center of asymmetry was in one of the groups attached to a carbonyl group. The later type of asymmetric reaction has been extensively studied[3]. Accordingly, emphasis was brought to study in more detail the occurance of partial asymmetric synthesis in the Reformatzky reaction. Palmer and Reid[4] found that the reaction of benzaldehyde with (–) –menthyl bromoacetate in a Reformatzky reaction gives, after hydrol lysis of the resulting ester, laevorotatory β–hydroxy β-phenylpropionic acid while the acid obtained with (–)–bornyl or with fenchyl bromoacetate is dextrorotatory. The optical yield of β-hydroxy-β-phenyl-propionic acid obtained is varied from 15 to 30 % according to the experimental conditions and to the catalyst used as well. Also, they stated that variations in, for example, the concentration of the reactants, the duration of heating the Reformatzky reaction mixture, and the zinc-ester-carbonyl compound ratios had little effect upon th specific rotation of the β-hydroxy acids obtained.

RESULTS AND DISCUSSION

In the present work trials were carried out for prepeating Palmer and Reid reaction of benzaldeyhyde or acetophenone under Reformatzky conditions but in the presence of sugar derivative for the sake of improving the optical yield of the β-hydroxy acid obtained. The purpose of using such sugar derivative is to provide excellent chiral frameworks for mechanistic studies of asymmetric synthesis and in addition (and perhaps of more importance) can serve as ready available and easily modified sources of asymmetric centers having known configuration for the synthesis of other important molecules. For example it is possible to (a) create a new asymmetric center within a carbohydrate framework, (b) establish the configuration of the new asymmetric center by spectroscopic or other appropriate technique, (c) detach the new asymmetric center from the carbohydrate framework by simple chemical reaction, and (d) incorporate it into a molecules of important interest. Consequently, ethyl 1,2: 5,6-di-0-isopropylideno- α-D- glucofuranosyl bromoacetate (I) was prepared analogusly to the procedure described by Kanawa and Emoto[5] for the purpose of using optically active bromoacetic ester instead of the optically inactive one.



I, R = $-CO-CH_2-Br$

II, R = H

III, R = $-CO-CH_2-CH(OH)C_6H_5$

Furthermore, the reaction of glucofuranosyl bromoacetate derivative I with benzaldehyde under Reformatzky conditions was studied. Thus, for the purpose of preparing optically active β–hydroxy-β-phenylpropionic acid, the glucofuranosyl bromoacetate derivative I (0 .1 mole) in ether-benzene mixture (1:1) was added in such a rate just to keep the reaction going on with the activated zinc (0.2 g- atom) in the same solvent mixture. The reaction mixture was refluxed for 2 hours. Benzaldehyde (0.2 mole) was added gradually to zinc reagent formed. The β–hydroxy–β–phenyl–propionic acid ester III was obtained by extraction with ether from the reaction medium according to the usual manner of working up described for Reformatzky reaction. This ester III was then hydrolysed by boiling it with alcoholic potassium hydroxide solution to give the desired β–hydroxy–β–phenylpropionic acid of specific rotation $[\alpha]_D = -4.52°$ (c 2 .51 in ethanol) (23 .78 % optical yield). It is worthy to mention that the specific rotation $[\alpha]_D$ according to Palmer and Reid[4] for β–hydroxy–β–phenylpropionic acid under almost the same experimental conditions mentioned above was –4 .39° (c 2 .63 in ethanol) (23 .11 % optical yield). In addition, it is obvious that the β–hydrxy–β–phenylpropionic acid produced by using glucofuranosyl bromoacetic ester I instead of menthyl bromoacetic ester has no remarkable increase in the optical yield besides there is no change in the sign of rotation of the β–hydroxy acid obtained. Consequently, similar experiment has now been carried out with acetophenone in place of benzaldehyde with a view to ascertain how far the degree of asymmetric synthesis is affected by substituting a methyl group for a hydrogen atom, and by the presence of a sugar derivative as well. Therefore, Reformatzky, reaction was done in a mixture of benzene-ether by using optically

inactive ethyl bromoacetate (0 .1 mole) and glucofuranose derivative II (0 .05 mole) (instead of the optically active glucofuranosyl bromoacetic ester I) in presence of activated zinc (0 .2 g–atom) and acetophenone (0 .05 mole) under the same experimental conditions described above for benzaldehyde. The β–hydroxy–β–phenylbutric acid obtained has specific rotation ($[\alpha]_D = -0.48°$ (c 2 .47 in ethanol) (5 .39 % optical yield). It is clear that the sign of rotation of β–hydroxy–β–phenyl butyric acid obtained is laevorotatory while that obtained by Palmer and Reid[6] is dextrorotatory and has $[\alpha]_D = 3.03°$ (c 7 .33 in ethanol) (34 .04 % optical yield). Accordingly, the use of sugar derivative in asymmetric synthesis of β–hydroxy acids following Reformatzky conditions is not promising.

EXPERIMENTAL

Zinc used was activated by boiling it at 100°C in a solution of few drops of concentrated nitric in concentrated sulphuric acid for 15 minutes. After cooling at room temperature the zinc was separated from the acid by filtration, then washed successively three times with distilled water, acetone and finally with anhydrous ether. After drying under vacuum at 100°C for 12 hr, it was then ready for use. Ethyl bromoacetate was distilled under reduces pressure and stored under nitrogen atmosphere. All carbonyl compounds were distilled shortly before use. The solvents used were water and halide free. Optical rotations were measured on a Zeiss-Visual polarometer with readings to $\pm$ 0 .02°, in ethanol at 25° C. The length of the tube being 1 dm, sodium light (D–line) was used. Specific rotations are $[\alpha]_D = -19.0°$ (EtOH) for (S) – (–) –3–hydroxy–3–phenylpropionic acid and $[\alpha]_D = +8.9°$ (EtOH) for (S) – (+) – 3–hydroxy–3–phenylbutyric acid[7,8].

Preparation of optically active β–hydroxy–β–phenylpropionic acid:

A 250 ml three-necked flack was fitted with an efficient reflux condenser, Teflon-covered magnetic stirring bar and a pressure-equalized dropping funnel. All materials were added to the apparatus under slight positive nitrogen pressure, and the reaction was run under anhydrous nitrogen atmosphere. In the flack were placed 5 .9 g (0 .09 g-atom) of zinc, 47 ml of anhydrous ether-benzene mixture (1:1) (henceforth referred to as the usual solvent) and few crystals of iodine. In the dropping funnel was placed a solution of glucofuranosyl bromoacetic ester I (0 .1 mole) in the usual solvent. Several drops of the ester solution was ad-

mitted to the flack while the material inside was heated to boilling. Every 10 minutes a few more drops of the ester solution was let into the flask until the reaction was initiated as indicated by disappearance of iodine colour and clouding of the reaction mixture. This usually occurred, between 5 and 30 minutes after refluxing started. Occasionally initiation was extremely sluggish. The ester solution was added while stirring in such a rate to keep the reaction going on (required 2 hr for complete addition). After 80 minutes from initiation another 4 g (0 .061 g-atom) of zinc was added to the reaction mixture and upon completion of the ester addition a final portion of 3 .2 g (0 .049 g-atom) of zinc was added, this brought the total amount of zinc to 13 .1 g (0 .2 g-atom). The reaction mixture was then refluxed for further 2 hours. A solution of benzaldehyde (0.2 mole) in 30 ml of the usual solvent was dropwise added to zinc reagent formed. After the addition was over, the mixture was then heated under reflux for further 2 hours. The reaction mixture was then chilled and poured onto 100 ml of chilled 10 % sulphuric acid solution. The layers were separated and the aqueous portion was extracted three times with a total of 150 ml of ether. The combined organic portions were washed three times with a total of 75 ml water and then dried over anhydrous sodium sulphate. Upon filtration and solvent distillation, the residue was hydrolyzed by boilling it in 2.5 N potassium hydroxide solution (22 ml) and 96% ethanol (50 ml) for 4 hours. The mixture was diluted with water (40 ml) and the alcohol was stripped of at 60 °C under reduced pressure. The aqueous residue was extracted with ether (3 x 25 ml) then acidified with 5 N sulphuric acid. The acidified aqueous solution was extracted with ether (3 x 25 ml). The ethereal extract was washed with water (3 x 10 ml) then dried over anhydrous sodium sulphate. Stripping off the ether gave, the crude β–hydroxy–β–phenylpropionic acid was purified through column chromatography (Wako Gel) using chloroform-hexane (1:1) as eluent. The pure β–hydroxy–β–phenylpropionic acid had m.p. 90°C and $[\alpha]_D = -4.52$ (c 2 .51 in ethanol).

β–Hydroxy–β–phenylbutryric acid was prepared by using the same experimental procedure described above but using ethyl bromoacetate (0 .1 mole), zinc (0 .2 g–atom), sugar derivative II (0 .05 mole) and acetophenone (0 .05 mole). The sugar derivative II was added to the organozinc reagent formed and stirred for an hour before the addition of acetophenone. The β–hydroxy–β– phenylbutyric acid was crystallized from ligroin, m.p. 71°C, $[\alpha]_D = -0.48°$ (c 2 .47 in ethanol).

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