1952

4-Benzoyl-4-methyl-1, 2-epoxypentane, An attempted synthesis

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4-BENZOYL-4-METHYL-1,2-EPOXYPENTANE,
AN ATTEMPTED SYNTHESIS
BY
ROBERT L. SNELL

A
THESIS
submitted to the faculty of the
UNIVERSITY OF MISSOURI SCHOOL OF MINES AND METALLURGY
in partial fulfillment of the work required for the
Degree of
MASTER OF SCIENCE, CHEMISTRY MAJOR
Rolla, Missouri
1952

Approved by Robert R. Russell
Assistant Professor of Chemical Engineering
ACKNOWLEDGMENT

The author wishes to thank Dr. Robert R. Russell for his suggestions and assistance during the course of this investigation.
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INTRODUCTION

The chemistry of the epoxide grouping is a subject that has not been fully explored. Russell, (unpublished) work), in making derivatives to characterize some compounds thought to contain a chain having a 1,2-epoxy-4-ketone grouping, found that a 2,4-dinitrophenylhydrazone formed in a peculiar manner. An elemental analysis of the derivative showed that it had lost two atoms of oxygen, rather than the expected one atom of oxygen. If this had happened, the most probable structure for the derivative would be a substituted six-membered ring containing two adjacent nitrogen atoms, and the epoxide oxygen would here have undergone a reaction ordinarily confined to a carbonyl oxygen. The reaction may be represented as follows:

\[
\begin{align*}
A_r - C^- C^- C^- C^- C^- C^- R^- + H_2NNH\left(\bigcirc\bigcirc\right)NO_2^- \rightarrow &
A_r - C^- C^- C^- C^- C^- C^- R^- + 2H_2O
\end{align*}
\]

A 2,4-dinitrophenylhydrazone is made in a ninety-five percent ethanol solution catalyzed with acid. Under these conditions an epoxide would be expected to react with the ethanol to form a hydroxy ether, or with the

(1) Swern, D., Billen, G., and Scanlan, J., Preparation of some Hydroxy-ethers from 9,10-Epoxystearic Acid and 9,10-Epoxyoctadecanol, J. Am. Chem. Soc., 70, 1228 (1948)
water present to form a glycol, or the epoxide group could survive unchanged, giving a normal ketone derivative.


This epoxy-ketone was prepared under drastic conditions, such that it is conceivable that the epoxy oxygen could have rearranged (isomerized.)

The object of this research was to prepare first the simplest homologue of the epoxy-ketone considered by Russell to have been his product. If this homologue, 4-benzoyl-4-methyl-1,2-epoxypentane, could be prepared and caused to form a cyclic derivative of the type given by 1,4-diketones with 2,4-dinitrophenylhydrazone, the organic chemist would be given a new approach to substituted 1,2-diazines as well as a previously unreported reaction of the epoxide grouping. If this reaction could be made to occur, other epoxides of this series would be prepared and treated in the same manner.

It was decided that the shortest route to 4-benzoyl-4-methyl-1, 2-epoxypentane would be the direct condensation of epichlorohydrin with isobutyrophenone.

(3) Mme. Ramart-Lucas and Haller, A., Compt. rend. 158, 1302 (1914)

There was also the possibility of condensing isobutyrophenone with allyl halides to produce 4-benzoyl-4-methyl-1-pentene. This could then be converted to
the halohydrin followed by treatment with base to form the epoxide, or it could be treated with a peracid to form the epoxide directly.
LITERATURE SURVEY

There is nothing in the literature concerning the reaction of an epoxide group with 2,4-dinitrophenylhydrazine to give a 2,4-dinitrophenylhydrazone type of derivative. (4)

It has been reported that sodamide suspended in an inert solvent, such as benzene, toluene, or ether, at reflux will react with isobutyrophenone at the alpha hydrogen to give ammonia and the sodium salt of the ketone. This product, without isolation, has been reported to react with various alkyl halides. The condensation product with epibromohydrin was reported to be oxypropylene-dimethylacetophenone (or 4-benzoyl-4-methyl-1,2-epoxy-pentane).

The sodium compound of isobutyrophenone has also been reported to react with allyl bromide to give 4-benzoyl-4-methyl-1-pentene.

Several workers have described the conversion of alkenes to halohydrins in good yields by treating aqueous suspensions of the alkene with bromine dissolved in aqueous potassium bromide solution. An example is the preparation of 1-chloro-3-bromo-2-methyl-2-propanol from methallyl chloride in 95% yield. (6)


There are numerous other methods for converting halohydrins to epoxides. It seemed desirable to not
use a method so drastic as refluxing the halohydrin with
sodium metal in anhydrous toluene, particularly because
this was the method used by Russell to obtain the
original compound considered to be the epoxy-ketone,
5-benzoyl-5-methyl-2,3-epoxyhexane.

The method of steam distilling the epoxide, as it
forms, from base is typified by the conversion of di-
chloro-tert-butyl alcohol to 1-chloro-2-methyl-2,3-
epoxypropane in 95% yield.

(7) Hearne and De Jong, Ind. and Eng. Chem. 33, 941(1941)

These authors reported that this reaction is complete
and quantitative in a few minutes, even at room temperature,
if an excess of base is present.

A common method for making epoxides is the treatment
of the corresponding alkene with a peracid. A typical
example is the formation of styrene oxide by treating
styrene with perbenzoic acid.

(8) Hibbert, H. and Burt, P., Organic syntheses,
New York, (1941)
Condensation of isobutyrophenone with epichlorohydrin (3)

The procedure for a typical experiment is described, though several runs were made in various solvents and with varying quantities of reactants.

In a three necked flask, fitted with stirrer, reflux condenser, and dropping funnel was suspended 39 g. (1 mol) of sodamide in 400 cc. of dry ether. The reflux condenser was fitted with a drying tube since the reaction had to be carried out under anhydrous conditions. The stirrer was started and left running throughout the course of the reaction. With the mixture refluxing, 170 g. (1.15 mols) of isobutyrophenone was added dropwise. The evolved ammonia was absorbed in acid and the increase in weight of the acid solution showed that after four hours the reaction was essentially complete. The solution was now brown (and in one run definitely contained a white precipitate).

One mole (92.5 g.) of epichlorohydrin was then added dropwise and the refluxing continued for ten hours. The reaction mixture was cooled, then poured into ice water and the two layers were separated. The aqueous layer was washed several times with ether and the combined ether extracts were washed twice with ice water, then dried over anhydrous sodium sulfate. The ether was distilled off and the residue was fractionated at reduced pressure.
The following fractions were collected:

(1) approximately 50 g. of isobutyrophenone
(2) approximately 2 cc., b.p. 100-135\(^{\circ}\)/12 mm
(3) 19 g., b.p. 137-140\(^{\circ}\)/12 mm; m.p. 59\(^{\circ}\)

Above 140\(^{\circ}\)/12 mm there was decomposition. A large quantity of tarry material remained.

The third fraction was that reported to be 4-benzoyl-4-methyl-1,2-epoxypentane. This material was tested for the epoxide group by treating it with pyridinium chloride in chloroform and titrating the excess hydrochloric acid. The compound, 2.0426 g., was treated with 25 cc. of 1.0044 N. pyridinium hydrochloride (with respect to HCl). The base required in titrating unreacted HCl was 51.6 cc. of 0.482N. sodium hydroxide, as compared with 52.0 cc. required for the total amount of hydrochloric acid used.


This material was also tested for functional groups. It did not give a 2,4-dinitrophenylhydrazone when catalyzed with either hydrochloric or sulfuric acids, indicating no reactive carbonyl oxygen. It did not show an active benzene ring when treated with aluminum chloride in carbon tetrachloride. It did not decolorize bromine in carbon tetrachloride, indicating
no reactive double bonds and no replaceable hydrogen. The material gave no test for halogen with alcoholic silver nitrate and did not give the iodoform reaction. It did react with water but the products were not obtained in a pure form, having a melting point range of 79-90°. The product reported from the reaction with water had a m.p. of 100° and was considered to be 4-benzoyl-4-methyl-1,2-pentanediol.

The presumed 4-benzoyl-4-methyl-1,2-epoxypentane contains no nitrogen or halogen. A reaction product, presumably the oxime, from treatment with hydroxylamine hydrochloride in pyridine was obtained, m.p. 128°, which did contain nitrogen and no halogen. The presumed 4-benzoyl-4-methyl-1,2-epoxypentane is soluble in 12N.HCl and on dilution with water white crystals form.

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A carbon, hydrogen analysis of the presumed 4-benzoyl-4-methyl-1,2-epoxypentane showed: C-76.15%, H-7.71% as compared with the calculated C-76.48%, H-7.89% if the compound were 4-benzoyl-4-methyl-1,2-epoxypentane.
Condensation of Isobutyrophenone with Bromoacetone

It seemed desirable to make the 1,4-diketone, 4-benzoyl-4-methyl-2-pentanone, which would be a likely product if the epoxide had isomerized. This diketone would be expected to give the same substituted diazine as the one expected if 4-benzoyl-4-methyl-1,2-epoxypentane did give a diazine with 2,4-dinitrophenylhydrazone.

Attempts to condense isobutyrophenone with bromoacetone using the sodamide method were unsuccessful.
Condensation of Isobutyrophenone with Allyl Bromide
4-Benzoyl-4-Methyl-1-Pentene (4)

In a three-necked flask equipped with stirrer, reflux condenser fitted with drying tube, and dropping funnel was suspended 80 g. (2 mols) of sodamide in 400 cc of anhydrous thiophene free benzene. To the stirred and refluxing mixture there was added all at once 296 g. (2 mols) of isobutyrophenone. The reaction became violent and required external cooling. It was stirred under reflux for six hours. The mixture was quite pasty and appeared to have a white solid suspended in a brown liquid.

The heat source was removed and 242 g. (2 mols) of allyl bromide was added with stirring at such a rate as to maintain refluxing. (During the addition the mixture became fluid again). After the addition was completed the mixture was refluxed with stirring for an additional half hour, then allowed to stand overnight at room temperature. The mixture was then poured into ice water, forming two layers. The benzene layer was separated, and the aqueous layer washed with benzene. The combined benzene solutions were washed with water, then dried over anhydrous sodium sulfate, and the benzene was removed. The residue was fractionated at reduced pressure, the separation of product from isobutyrophenone requiring several fractionations. The following fractions were collected:

(1) 83 g. of isobutyrophenone
(2) Approximately 50 g. distilling 118-130°/15 mm.

(3) 170 g., 130-133°/15 mm.

The yield of 4-benzoyl-4-methyl-1-pentene was 63% based on unrecovered isobutyrophenone. The product showed no nitrogen or halogen.

A sample of the product boiling 131-132°/15 mm., \( n_D^{20} 1.5198 \), was taken for derivatives. The 2,4-dinitrophenylhydrazone melts 103-104°.
4-Benzoyl-4-Methyl-2-Hydroxy-1-Bromopentane

There was suspended in 300 cc of water 93 g. (0.49 mols) of 4-benzoyl-4-methyl-1-pentene. To this was added, with vigorous stirring, 33 cc of bromine dissolved in a solution of 45 g. of potassium bromide in 200 cc of water, dropwise at such a rate that the solution remained at room temperature and there was no excess bromine present. At the end of two and one half hours there was an excess of bromine in the mixture, though not quite all of the bromine had been added. The product was a white, crystalline solid which was filtered out, washed with water, then triturated with sodium bicarbonate solution, and finally filtered and washed again with water. The crude solid melted around 100°. A recrystallization was attempted from various solvents but only an oil could be obtained, though a small sample of the oil did crystallize after two weeks. The oil was used in subsequent reactions.
4-Benzoyl-4-Methyl-1,2-Epoxypentane

An attempt was made to steam distill the epoxide at reduced pressure by allowing 4-benzoyl-4-methyl-2-hydroxy-1-bromopentane to drip into a stirred, distilling, aqueous lime suspension, when 500 cc. of water had been collected with no organic material coming over, the attempt was abandoned.

Another attempt was to produce this epoxide by reaction with aqueous base, followed by an extraction of the organic material.

About 0.25 mols of 4-benzoyl-4-methyl-2-hydroxy-1-bromopentane in the form of an oil was violently shaken with aqueous base but there was no apparent reaction and most of the oil did not emulsify. Enough dioxane was added to obtain an emulsion on violent shaking. A slight temperature rise indicated that reaction had occurred. The mixture was then extracted with petroleum ether and with benzene, and these extracts washed with water, dried over anhydrous sodium sulfate, solvent removed and the residue distilled.

There was collected 12 g., b.p. 164-165°/13 mm.,

$\eta^0_D = 1.5280$.

This material did not decolorize bromine in carbon tetrachloride, though it did decolorize permanganate in acetone slightly more rapidly than a blank. (Styrene oxide in acetone also decolorized permanganate slightly more rapidly than an acetone blank). When the material
was shaken with 12 N. HCl a solid was obtained. The product also gives a 2,4-dinitrophenylhydrazone which softens at 210° and is decomposed by 225°. It is likely that the true melting point could be found if the 2,4-dinitrophenylhydrazone were not exposed to this high temperature for so long a time.

It seems unlikely that 4-benzoyl-4-methyl-1,2-epoxypentane would have so high a boiling point as this product has. This product also does not give a pyridinium chloride test for epoxy oxygen.
4-Benzoyl-4-Methyl-1,2-Epoxypentane

It seemed unlikely that the epoxy-ketone had been prepared, therefore an attempt was made using the perbenzoic acid method as applied to the preparation of styrene oxide. (8)

The perbenzoic acid was prepared by a standard method. (11)


A solution of 10.4 g. (0.44 g. atoms) of sodium in 200 cc. of methanol was cooled to 0-(-)5°, and to this was added 100 g. (0.42 mols) of benzoyl peroxide in 400 cc. of chloroform at 0°. The temperatures of all the solutions in the whole experiment were maintained as nearly 0° as possible. After ten minutes of shaking the mixture became milky. It was then transferred to a separatory funnel and washed with 1 liter of water containing crushed ice. The aqueous layer was saved and washed twice with 200 cc. portions of cold chloroform, then acidified with 450 cc. of cold 1 N. sulfuric acid. The liberated perbenzoic acid was then extracted with several portions of cold chloroform. The combined chloroform extracts were dried over anhydrous sodium sulfate, the drying agent was filtered out and the perbenzoic acid solution used without further treatment.

It seemed reasonable to assume that an excess of peracid would leave no unreacted alkene, thus making
isolation of the epoxide easier, and would not cause undesirable side reactions.

To the perbenzoic acid solution, still at 0°, was added 38 g. (0.2 mols) of 4-benzoyl-4-methyl-1-pentene with shaking. The mixture was kept at 0° for twenty-four hours with occasional shaking. It was then extracted twice with 10% sodium hydroxide solution at 0°, washed with ice water until neutral to litmus and dried over anhydrous sodium sulfate. The drying agent was filtered out and the chloroform removed on a steam bath. White crystals formed and were filtered out, and the residue distilled to 170°/16 mm. Some solid came over, was filtered out and added to the previously collected solid. The distillate was then fractionated. More white solid was collected and 21 g. of the starting alkene, so that the white solid proved to be the only product, other than tar. Six grams of solid was recovered after recrystallization from petroleum ether. The solid did not give a sharp melting point, most of the material melting 176-180° but a small amount remained unmelted.

The white solid does not give an epoxide test with pyridinium chloride for the excess HCl again proved to be the total amount used in the test.

The reaction was repeated, using more alkene, 50 g. (0.28 mols), with the same results.
Pyridinium Chloride-Chloroform Test for Epoxides (9)

This method is intended for the determination of epichlorohydrin content of epichlorohydrin. It is applicable to other epoxy compounds which do not contain water, aldehydes or easily hydrolyzed chlorohydrins.

The sample is reacted with pyridinium chloride in chloroform at 100°, converting the epoxide to a chlorohydrin. The amount of acid as determined by back titration with standard base, is a measure of the epoxide content of the sample.

To prepare approximately one liter of solution:
Weigh 75 g. of c.p. anhydrous pyridine into a one liter Erlenmeyer flask, add about 400 ml. of anhydrous c.p. chloroform and weigh to the nearest gram. Place the flask into an ice bath and slowly bubble in anhydrous hydrogen chloride gas until 35 g. have been admitted (determined by weighing flask at intervals). Transfer mixture to a 2 liter graduated cylinder and warm to room temperature. Agitate well and expel the HCl vapors from the cylinder with a stream of dry air. Add a 10 ml. aliquot of the solution to 50-75 ml. of c.p. methanol in a 250 ml. Erlenmeyer flask and titrate to the phenolphthalein end point with standard 0.5N NaOH. Calculate the amount of pyridine to be added in order to neutralize the free hydrogen chloride, if any, and to obtain a 5 per cent excess, using the following equation:
(S)(N)(V)(79.1)(1.05) \frac{-W}{1000 \ A} = g. pyridine to be added.

where:

- \( S \) = volume of NaOH solution, used in titrating aliquot, ml.
- \( N \) = normality of NaOH solution.
- \( V \) = total volume of mixture after aliquot has been taken, ml.
- \( A \) = volume of aliquot, ml.
- \( W \) = wt. of pyridine, g. added initially.

Add the calculated amount of pyridine and dilute the solution with chloroform to a total volume of \( \frac{(S)(N)(V)}{A} \) ml.

To verify that the reagent has been properly prepared, titrate 25 ml. of reagent with 0.5N NaOH, preparing as for a blank (see below). Titrate another 25 ml. of reagent after refluxing 15 minutes. The two titrations should agree within 0.1 ml. of titrant.

Use a quantity of sample equivalent to approximately 0.010 to 0.013 moles of the epoxy compound.

Procedure: Place a handful of glass beads in a pressure bottle, add 25 ml. of the pyridinium chloride reagent, introduce the weighed sample (in a sealed ampoule) into the bottle, seal the bottle and break the ampoule by shaking the bottle. Place the bottle in a steam bath at 100° and allow the reaction to go for an hour before removing the bottle and slowly cooling it to room temperature. The bottle is opened when cool to release the vacuum, immersed in an ice bath til cold, 75 ml. of c.p. methanol is added and the bottle again chilled. One ml. of 1.0% phenolphthalein in 60% ethanol is added and the sample titrated with 0.5 N
sodium hydroxide to a definite pink end point that will persist at least 30 seconds. Keep the bottle in an ice bath while titrating and agitate continuously. When near the end point, stopper the bottle and shake. A blank should be run omitting the sample and using 100ml. of methanol instead of 75.

The percent weight of the epoxy compound is found by means of the equation:

$$\% \text{ w of epoxide} = \frac{(B - V)(N)(E)}{10W}$$

where:

- $V$ = volume of NaOH used to titrate sample, ml.
- $B$ = volume of NaOH used to titrate blank, ml.
- $N$ = normality of NaOH
- $E$ = equivalent weight of the epoxide
- $W$ = weight of sample, grams
Conclusions

The compound resulting from the attempted condensation of isobutyrophenone and epichlorohydrin and reported to be 4-benzoyl-4-methyl-1,2-epoxypentane, does not give an epoxide test with pyridinium chloride, either because it is not an epoxide or because the test is not applicable, though the carbon, hydrogen analysis indicates that it is the epoxide or an isomer.

The product resulting from the attempted epoxidation of 4-benzoyl-4-methyl-2-hydroxy-1-bromopentane has a higher boiling point than expected for the epoxide.

The product resulting from the attempted peracid epoxidation of 4-benzoyl-4-methyl-1-pentene is definitely not the epoxide. It did not give an epoxide test and it does not have suitable physical properties.

It is noteworthy that the three methods should each produce the epoxide, and that the corresponding glycol is the only other likely product, but each method produced a different compound.

It seems unwise, with the data at hand, to state the composition of any of the three products before making further studies such as infrared absorption spectra.
Suggestions for Further Work

It would be desirable to study further the epoxidation of 4-benzoyl-4-methyl-1-pentene with peracids, for the method should work. Possibly the reaction, as described, should be run using no excess of perbenzoic acid, since it is possible that excess peracid could bring about conversion to the glycol.

It would also be desirable to determine in some way the exact structure of the compound reported to be 4-benzoyl-4-methyl-1-pentene.

The reaction products that were obtained in this work should be identified, possibly by infrared absorption spectra.
Bibliography


(3) Haller and Bauer, Compt. rend. 148, 70 (1909).

(4) Haller and Bauer, Compt. rend. 158, 825 (1914).

(5) Hearne and De Jong, Ind. and Eng. Chem. 33, 941 (1941).


(8) Ramart-Lucas and Haller, Compt. rend. 158, 1302 (1914).


Robert L. Snell was born on January 28, 1925, at El Dorado Springs, Missouri. He attended various schools, graduated from El Dorado Springs High School in 1941.

Mr. Snell attended Drury College and Southwest Missouri State in Springfield, Missouri.

He was inducted into the Army Air Force in September, 1943. After receiving training at various schools he was assigned to the 4th Air Force as a radio operator until his discharge on March 9, 1946.

He then returned to Drury College and completed the requirements for a Bachelor of Science degree in Chemistry in June, 1948.

In September, 1948, he enrolled in the Graduate School of the Missouri School of Mines and Metallurgy and assumed the duties of an Instructor in the Chemical Engineering Department.