[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

GAMMA-CHLOROPROPYL-PHENYLKETONE

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Relatively few γ-halogen ketones are recorded in the literature. The only general methods of preparing them seem to be by the action of halogen acids on acyl cyclopropanes[1] and by Wohlgemuth's method[2] by the action of organo-zinc halides on γ-halogen acid chlorides. In connection with the measurement of the reactivity of the halogen atoms in organic compounds, we desired to prepare the unknown γ-chloropropyl-phenylketone in order to compare it with α- and β-chloroketones.[3] We were also interested in this compound because of the possibility of converting it into benzoyl-cyclopropane. Since we hoped to carry out experiments involving considerable quantities of this latter substance which is not easily synthesized by the known methods, it seemed worth while to attempt to develop a method of preparing γ-chloropropyl-phenylketone in quantity from some readily accessible raw material. Trimethylene glycol seemed a promising starting point, as from it γ-chloro-butyronitrile can be prepared, and if the action of phenylmagnesium bromide could be confined to the nitrile group, the synthesis would be accomplished. Our expectations were realized and the preparation of γ-chloropropyl-phenylketone and benzoyl-cyclopropane can be carried out in this way, although the yields leave much to be desired.

The results of numerous experiments on each step of the following synthesis can be briefly summarized as follows.

$$CH_2OHCH_2CH_2OH \xrightarrow{HCl} CH_2OHCH_2CH_2Cl \quad (1)$$

$$CH_2OHCH_2CH_2Cl \xrightarrow{HBr} CH_2ClCH_2CH_2Br \quad (2)$$

$$CH_2ClCH_2CH_2Br \xrightarrow{KCN} CH_2ClCH_2CH_2CN \quad (3)$$

$$CH_2ClCH_2CH_2CN \xrightarrow{C_6H_5MgBr} CH_2ClCH_2CH_2COC_6H_5 \quad (4)$$

The yield in the first step varied, but was generally over 65%; the preparation of the chlorobromide could be readily carried out with 70% yields; the average yield of nitrile on the third step was 42%, while the last transformation involving the addition of the Grignard reagent and hydrolysis of the imide resulted in a 50% yield. Thus the final amount of the product was only about 9% of the amount calculated from the glycol; in spite

[1] (a) Lipp, *Ber.*, **22,** 1206 (1889); (b) Perkins, *J. Chem. Soc.*, **59,** 876 (1891).

[2] Wohlgemuth, *Ann. chim.*, [9] **2,** 292, 403 (1914); **3,** 141 (1915); *J. prakt. Chem.*, **103,** 391 (1922).

[3] Conant and Kirner, THIS JOURNAL, **46,** 232 (1924); the measurements of the reactivity of γ-chloropropyl-phenylketone with potassium iodide in absolute acetone are recorded in this paper.

of this, the process has much to recommend it, as the materials are cheap and the procedure relatively simple and rapid. The fact that the nitrile of a halogenated acid yields a halogenated ketone on treatment with a Grignard reagent appears to be a new observation which may make possible other syntheses of this type. Bruylants[4] found that the action of ethyl-magnesium bromide on γ-bromo-butyronitrile gave among other products (all free from halogen) considerable amounts of ethyl-cyclopropyl ketone. Possibly a similar reaction involving the formation of benzoyl-cyclopropane may account for the 50% yield in the last step of our synthesis. Bruylants allowed his reaction to take place vigorously at room temperature with an excess of Grignard reagent while we operated cautiously at 0°; this difference in procedure may account for the fact that we confined the action of the Grignard reagent to the nitrile group. If this is so, a similar procedure should make possible the synthesis of other halogenated ketones by the use of alkyl as well as aryl magnesium halides.

Lipp[5] and more recently Wohlgemuth[2] have shown that γ-halogen ketones on treatment with solid potassium hydroxide at 140–170° form cyclopropane ketones. By the action of potassium hydroxide in methyl alcohol solution on γ-chloropropyl-phenylketone at room temperature for 18 hours we obtained a good yield of benzoyl-cyclopropane. The action of potassium acetate in alcohol solution either at room temperature or at the boiling point caused the elimination of considerable amounts of hydrogen chloride from the compound but the action was not complete; even after boiling the materials for nine hours, the product still contained halogen and distilled over a wide range. The identity of benzoyl-cyclopropane was established by preparing the crystalline oxime and semicarbazone reported by earlier investigators.[6]

Phenylhydrazine reacts with γ-chloropropyl-phenylketone at room temperature in alcoholic solution to form a crystalline pyridazine derivative; this is the best method of identifying the chloroketone.[7]

Experimental Part

Preparation of Trimethylene Chlorobromide.—Trimethylene glycol was converted into the chlorohydrin by the action of dry hydrogen chloride at 160–170° according to the detailed directions of Adams and Marvel.[8] When the directions were carefully followed, particularly in regard to the necessity of a very rapid stream of hydrogen chloride, yields compar-

[4] Bruylants, *Rec. trav. chim.*, **28,** 238 (1909).

[5] Ref. 1 a, p. 1196.

[6] (a) Marshall and Perkin, *J. Chem. Soc.*, **59,** 887 (1891). (b) Kishner, *Chem. Zentr.*, **83,** 1458 (1912).

[7] Compare Wohlgemuth, Ref. 2.

[8] "Organic Chemical Reagents, III," R. Adams and C. S. Marvel, *Univ. Illinois Bull.*, Urbana, Illinois, **1921.**

able to those stated were obtained (65–70%). The chlorohydrin was heated with two equivalents of hydrobromic acid and sulfuric acid under a return condenser for one hour and the mixture was then distilled;[9] the average yield of chlorobromide was 70%.

Preparation of γ-Chloro-butyronitrile.—The procedure of Gabriel[10] can be somewhat improved by using only enough alcohol to make a homogeneous solution of the concentrated aqueous sodium cyanide solution and the trimethylene chlorobromide; the yield is not affected by this change and the product is much more easily recovered. Some glutaryl nitrile is always formed and a certain amount of chlorobromide is recovered unchanged. If the nitrile is desired as a by-product, the final distillation should be carried out under diminished pressure. A typical experiment was as follows.

A mixture of 256 g. of trimethylene chlorobromide with 500 cc. of alcohol and a solution of 102 g. of potassium cyanide in 160 cc. of water was boiled under a return condenser for 1.5 hours, and diluted with water. To aid the separation of the oil a small amount of chloroform was added and the chloroform layer dried and distilled under diminished pressure; 78 g. of chloronitrile was collected between 70° and 92° at 7 mm., the main portion boiling constantly at 85°; 10 g. of glutaryl nitrile boiling at 130–180° at 7 mm. was also obtained; yield of chloronitrile, 44.5%.

γ-Chloropropyl-phenylketone

In a typical experiment, a solution of 13 g. of γ-chloro-butyronitrile in 100 cc. of dry ether was slowly added to an ethereal solution of phenylmagnesium bromide prepared from 5.2 g. of magnesium and 40 g. of bromobenzene; the reaction mixture was kept cold in an ice-bath. After two to four hours the mixture had become a pasty mass and was poured into a mixture of ice and hydrochloric acid and immediately extracted with ether. This extraction removed any unchanged bromobenzene, benzene or diphenyl, and the first product of the reaction (which was the imide, $C_6H_5C(=NH)CH_2CH_2CH_2Cl$) stayed in the aqueous solution as the hydrochloride. This imide was only slowly hydrolyzed to the ketone in the ice-cold solution, but on allowing the solution to come to room temperature and to stand for 24 hours the hydrolysis was complete and the ketone separated as a dark brown oil. This was dissolved in ether, dried and distilled under diminished pressure; 12 g. of a light yellow oil was collected between 135° and 150° at 11 mm. (most of this boiled at 133.5–135°); yield, 54%. It was difficult to purify the compound completely by fractional distillation but it could be obtained very pure by recrystallizing it from anhydrous petroleum ether at —20°. It separated from a fairly dilute solution in the form of glistening white rosets. These were filtered off with suction on a funnel surrounded with ice and dried in a vacuum desiccator over paraffin and sulfuric acid; m. p., 19–20°.

Anal. Calc. for $C_{10}H_{11}OCl$: Cl, 19.42. Found: 19.39.

It is insoluble in water, slightly soluble in petroleum ether and readily soluble in alcohol and ether; it has no lachrymatory properties, in contrast to α-chloroketones.

1,3-Diphenyl-tetrahydro-pyridazine, $C_6H_5\overline{NCH_2CH_2CH=C}C_6H_5$ (NH bridging N and C).—Four g. of crude chloroketone, 6 g. of phenylhydrazine hydrochloride and 30 g. of potassium acetate were

[9] Kamm and Marvel, This Journal, **42**, 298 (1920).

[10] Gabriel, *Ber.*, **23**, 1771 (1890).

dissolved in 25 cc. of water and 75 cc. of ethyl alcohol. The mixture was allowed to stand for nine days and the crystalline precipitate then collected on a filter. The crude product melted at 138–140° and after crystallization from alcohol melted at 138–139°.

Anal. Calc. for $C_{16}H_{16}N_2$: N, 11.9. Found: 12.1.

Preparation of Benzoyl-cyclopropane.—Ten g. of chloroketone was mixed with a solution of 11.3 g. of potassium hydroxide in 130 cc. of methyl alcohol; after 18 hours, about half the alcohol was distilled and the residue diluted with water and extracted with ether. The ether was dried and distilled and the residual oil distilled under diminished pressure, passing over almost completely at 140–142° (37 mm.); yield, 5.5 g. Its identity as benzoyl-cyclopropane was established by the following experiments.

a. On treatment with semicarbazine hydrochloride and potassium acetate in alcohol at room temperature for 12 hours, a solid product was obtained which after crystallization melted at 182–183° (Kishner[6b] gives 185°).

b. Treated with hydroxylamine hydrochloride and potassium hydroxide in alcohol at room temperature, an oil was obtained which soon crystallized and after recrystallizing from petroleum ether melted at 90–94° (Perkin[6a] gives 90–92°; Kishner,[6b] 86–89°).

c. Bromine in carbon tetrachloride was without action on the substance except in the sunlight when the bromine color slowly disappeared and hydrobromic acid was evolved.

Summary

γ-Chloropropyl-phenylketone was synthesized by the action of phenylmagnesium bromide on γ-chloro-butyronitrile which can be prepared from trimethylene glycol without much difficulty. On treatment with potassium hydroxide in alcohol, the chloroketone is transformed into benzoyl-cyclopropane.

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STUDIES ON ENZYME ACTION. XXVIII
THE SPONTANEOUS INCREASE IN THE ACTIVITIES OF LIPASE AND PROTEASE OF TISSUE EXTRACTS

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Introduction

It was shown in an earlier paper[1] that the sucrase activity of banana extracts on standing increased for a certain period of time and then decreased again. The increases amounted to 40 to 100% of the original activities, were independent of the compositions of the extracting solutions and of the preservative used, were not due to the presence of banana cells or bacteria, and were not accounted for by changes in hydrogen-ion concentration. The natures and amounts of increases were found, however, to be dependent upon the state of ripeness of the bananas when

[1] McGuire and Falk, THIS JOURNAL, **45**, 1539 (1923).