

**BETA-PHENYLISOBUTYLMETHYL KETONE AND ITS
DERIVATIVES. THE SYNTHESIS OF ALPHA- AND OF BETA-
PHENYLISOVALERIC ACIDS**

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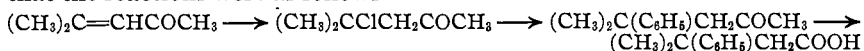
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When mesityl oxide is added to benzene in the presence of anhydrous aluminum chloride, condensation takes place with the formation of a ketone $C_{12}H_{16}O$. It is likely that the hydrogen chloride addition product of mesityl oxide is formed first and then reacts with the aluminum chloride setting free hydrogen chloride. Thus a trace of hydrogen chloride catalyzes the reaction and an evolution of the free gas takes place only at the very end.

The presence of the carbonyl group in the new substance is shown by the formation of the oxime and the semicarbazone. If the latter, which is formed quantitatively, is fractionally crystallized, all fractions have the same melting point, showing that the ketone is a single substance and not a mixture of isomers.

As a methyl ketone it is easily oxidized by sodium hypobromite solution with the formation of a phenylisovaleric acid which is identical with the one prepared by Eijkman¹ by the action of benzene on β,β -dimethylacrylic acid in the presence of aluminum chloride and characterized by a nitro derivative melting at 175° . In order to decide between the alpha and the beta forms of the acid, Eijkman treated his substance with benzaldehyde under the most varied conditions. As he failed to obtain any indication of a condensation, he inferred that there was no methylene group adjacent to the carboxyl group and that therefore his acid was the alpha form. This is not what might be expected in the present case. The chlorine of the addition product of mesityl oxide and hydrogen chloride has for good reasons been considered attached to the tertiary carbon atom, so that after replacement with phenyl and oxidation, β -phenylisovaleric acid should be obtained. In order to decide the question, both alpha and beta acids were prepared by the malonic ester method. The results, as shown in the experimental part, give conclusive proof that the acid obtained from the ketone, and therefore also Eijkman's acid, is the beta form and that the reactions were as follows



β -Phenylisobutyl methyl ketone does not react with sodium bisulfite. With a mixture of nitric and sulfuric acids it gives a nitro compound, which is soluble in sodium carbonate solution with a blood-red color. It is likely that this compound, which was not isolated in a pure state, contains a nitro group attached to an aliphatic carbon atom. Treated with

¹ Eijkman, *Chem. Centr.*, II, 1100 (1908).

an excess of bromine in acetic acid, the ketone gives a crystalline tetra-bromo derivative.

Of interest is the action of the ketone on heating with anhydrous zinc chloride. A mixture of hydrocarbons is obtained from which it is possible to isolate in fairly good yield a well-crystallizing substance melting at 130.5–131°. According to boiling point, molecular weight determination and analysis its formula is $C_{24}H_{28}$. It is therefore formed from two molecules of water. The hydrocarbon does not react with bromine in chloroform solution, even on heating or with the addition of iron powder or iodine. Boiled with concentrated nitric acid it gives a trinitro derivative, which is not soluble in sodium carbonate solution. Toward oxidizing agents the hydrocarbon is very resistant. Thus boiling with dilute nitric acid is without effect. Chromic acid in glacial acetic acid solution does not act in the cold; on boiling the solution slowly turns green. Most of the hydrocarbon remains intact; the rest seems to be completely oxidized, as no products such as benzoic acid or ketones could be isolated. Permanganate in moist acetone solution is not decolorized in the cold.

Boiling with aqueous permanganate for 142 hours gave but a small amount of manganese dioxide. The hydrocarbon was likewise unaffected by grinding with manganese dioxide and 50% sulfuric acid at 50°. According to these results about all that can be said as to the constitution of the hydrocarbon is that it is a very stable, saturated substance, probably of a cyclic nature.

The ketone may be reduced in the usual way with sodium and alcohol to form the corresponding alcohol, β -phenylisobutylmethylcarbinol.

On treatment with zinc chloride, this alcohol loses a molecule of water, giving the hydrocarbon $C_{12}H_{16}$. The latter is unsaturated and easily oxidized in contact with air. Attempts to purify such material by distillation over sodium resulted in the loss of most of it by polymerization. It probably has the structure $(CH_3)_2C(C_6H_5)CH=CHCH_3$. Attempts to prove this by means of the oxidation products with chromic acid were not successful. A complicated mixture of ketones was obtained which was separated into fractions; these were converted into semicarbazones and recrystallized. Acetophenone was identified by mixed melting point; phenylacetone and propiophenone were absent. A special search was made for α -phenylisobutyraldehyde in the fraction boiling around 110° (14 mm.). This fraction, however, did not reduce ammoniacal silver solution, nor could a high-melting semicarbazone be obtained.

Experimental Part

Preparation of β -Phenylisobutyl Methyl Ketone.—Ninety grams of anhydrous aluminum chloride in granular form together with 200 cc. of benzene is placed in a 500-cc. wide-mouthed Erlenmeyer flask. The latter is provided with a short vent-tube and a stirrer and cooled with water. Fifty grams of mesityl oxide is dropped in during an

hour with thorough stirring, which is then continued for three hours longer. The mixture is poured on ice and the water separated. The oil is washed with water, filtered, poured into sodium carbonate solution and steam distilled to remove the excess benzene. The ketone itself is but slightly volatile with steam. After cooling, the oil is separated, dried over calcium chloride and distilled under diminished pressure; yield, 72 g.; calcd., 89 g. The product boils at 124° (14 mm.) and is pure enough for preparative purposes. It contains, however, a trace of halogen and discolors after standing for some time. In order to purify it, the semicarbazone is prepared, recrystallized and steam distilled with a large excess of phthalic anhydride. The ketone thus obtained is a water-white, highly refractive liquid which remains colorless indefinitely. The odor is somewhat like that of camphor, with a suggestion of roses; b. p. 134° (22 mm.); 252° corr. (760 mm.); sp. gr. 25°/25°, 0.972.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.8; H, 9.09. Found: C, 81.5; H, 9.00.

Preparation of the Semicarbazone.—Twenty-five grams of ketone was added to a concentrated aqueous solution of 17 g. of semicarbazide hydrochloride and 22 g. of crystallized sodium acetate with the addition of enough methyl alcohol to render the mixture homogeneous. After standing for twenty-four hours the product was recrystallized from methyl alcohol; yield, 31 g.; m. p., 163–164°.

Anal. Calcd. for $C_{13}H_{18}ON_3$: N, 18.03. Found: N, 18.33.

Preparation of the Oxime.—Ten and seven-tenths grams of ketone was treated with an aqueous solution of 4.5 g. of hydroxylamine hydrochloride, 5.4 g. of sodium bicarbonate and enough methyl alcohol to render it homogeneous. After standing for several hours at 50°, the product was poured into water, extracted with ether and distilled under diminished pressure; yield, 9.3 g.; b. p. 181° (27 mm.); m. p. 52–54° (not recrystallized).

Anal. Calcd. for $C_{12}H_{17}ON$: N, 7.33. Found: N, 7.7.

Preparation of the Tetrabromo Ketone.—The ketone reacts with bromine with explosive violence and therefore a diluent is necessary; 8.8 g. of ketone in 20 cc. of glacial acetic acid is gradually treated with 35 g. of bromine. After standing for a day, water is added, the red oil taken up with ether and washed with sodium bisulfite solution to remove excess bromine. The ether is evaporated and the residue recrystallized from methyl alcohol; it gives a crystalline, white powder; m. p. 96–98°.

Anal. Calcd. for $C_{12}H_{12}OBr_4$: Br, 65.0. Found: Br, 64.9.

Preparation of the Hydrocarbon, $C_{24}H_{28}$.—Sixteen and seven-tenths grams of ketone and 12 g. of anhydrous zinc chloride were heated in a small Erlenmeyer flask on a gauze over a free flame. The zinc chloride slowly dissolved and the mixture turned a vivid carmine. At about 180° a lively reaction took place and the liquid divided into two layers. On cooling, both layers solidified. The upper, white crystalline layer was dissolved in petroleum ether and distilled under diminished pressure. The use of an Anschütz flask is advisable for this as the distillate has a tendency to solidify and clog up the side-neck. The fraction boiling from 150–230° (18 mm.) (8.6 g.) was pressed out between filter paper and recrystallized from petroleum ether; b. p. 195° (18 mm.); m. p. 130.5–131° corr. The material crystallized well in flat, white needles or plates.

Anal. Calcd. for $C_{24}H_{28}$: C, 91.1; H, 8.9. Found: C, 90.8; H, 8.8. *Mol. wt.* 0.021 g. of subs. in 0.132 g. of camphor gave 20° depression of melting point. Calcd. for $C_{24}H_{28}$: mol. wt., 316. Found: 318.

Preparation of Trinitrohydrocarbon.—Two grams of hydrocarbon was refluxed with 30 cc. of nitric acid (1.42) for nine hours. The oil finally dissolved without noticeable reaction but separated again on cooling. It was washed with water and recrystallized from much methyl alcohol; yield, 0.3 g. as fine white needles; m. p. 180–184°.

Anal. Calcd. for $C_{24}H_{28}(NO_2)_3$: N, 9.3. Found: N, 9.03.

Reduction of Ketone.—Ten grams of ketone was refluxed with 100 cc. of absolute alcohol in a one-liter flask and 20 g. of sodium was added rapidly through the condenser. After the reaction had quieted, 50 cc. more alcohol was added to dissolve the excess sodium. Then 68 cc. of water was added and the ethyl alcohol distilled off in an oil-bath. Water was added to the residue, the carbinol extracted with ether and distilled under diminished pressure; yield, 9.2 g.; b. p. 132–133° (17 mm.), sp. gr. 25°/25°, 0.960. It has little odor.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.89; H, 10.1. Found: C, 80.32; H, 9.9.

Dehydration of the Carbinol.—Seventeen and seven-tenths grams of the alcohol was heated with 14.5 g. of anhydrous zinc chloride over a free flame for one and one-half hours. After a slight reaction the mixture separated into two layers. After cooling, the upper layer was poured off and distilled; yield, 14.2 g.; b. p. 96–98° (17 mm.); sp. gr. 25°/25°, 0.889.

Anal. Calcd. for $C_{12}H_{14}$: C, 90.0; H, 10.0. Found: C, 88.1; H, 9.73.

The product was evidently not quite pure; it reacted instantly with bromine in chloroform. On oxidation with chromic acid in acetic acid solution, a complicated mixture was obtained boiling from 90° (18 mm.) to 150° (24 mm.). On recrystallizing the semicarbazones of the various fractions the only one identified was a small fraction of m. p. 186–189°. Mixed with acetophenone semicarbazone it melted at 187–189°.

Oxidation of the Ketone to β -Phenylisovaleric Acid.—Seventeen and six-tenths grams of ketone was shaken with sodium hypobromite solution prepared from 24 g. of sodium hydroxide, 48 g. of bromine and 100 g. of ice and water. The mixture became warm after about five hours and at the end of 20 hours the reaction was complete. After separating the bromoform and filtering, the aqueous solution was acidified with dilute sulfuric acid with the addition of a little sodium bisulfite. An oil separated which solidified on standing. It was pressed out between filter paper to remove oily impurities and recrystallized from petroleum ether; yield, 11.2 g.; m. p., 58–58.5°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.86. Found: C, 73.9; H, 7.9.

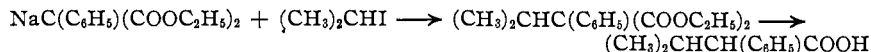
The nitro derivative, prepared by heating with 75% nitric acid, melts at 169–172°.

The methyl ester boils 120° (11 mm.); 123° (12 mm.).

The anilide was prepared as follows for the purpose of further comparison with the synthetic α - and β -acids: 1.5 g. of acid and 2.3 g. of aniline were heated for nine hours in a small distilling flask in a graphite bath so that water and aniline slowly distilled off. The product was dissolved in ether, shaking out with dilute sulfuric acid and with sodium carbonate solution, the ether removed and the residue recrystallized from 60% methyl alcohol with the use of bone black; m. p., 122–123°.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.6; H, 7.5. Found: C, 80.5; H, 7.2.

α -Phenylisovaleric Acid.—The ethyl ester of phenylacetic acid was condensed with ethyl oxalate by means of alcohol-free sodium ethylate to form phenylloxalacetic ester. This, on heating, lost carbon monoxide, giving phenylmalonic ester. This method² is not very satisfactory, so it is welcome that a new method has recently appeared.³ As found by Nelson and Cretcher in a similar case, the alkylation of phenylmalonic ester does not work well, much phenylacetic ester being formed. Eighteen and nine-tenths grams of phenylmalonic ester was added to a solution of 1.85 g. of sodium in 35 cc. of absolute alcohol and 25 g. of *isopropyl iodide* run in.



² W. Wislicenus, *Ber.*, **27**, 1093 (1894).

³ W. L. Nelson and L. H. Cretcher, *THIS JOURNAL*, **50**, 2758 (1928).

The solution remained clear until heated and then slowly became cloudy. After boiling for fourteen hours it had become neutral. The alcohol was distilled off, water added, the product extracted with ether and distilled; yield, 12.3 g.; b. p., 165–190° (31 mm.). According to analysis it was a mixture of about one part of phenylacetic ester with three parts of *isopropylphenylmalonic* ester. Boiled with a solution of 16 g. of potassium hydroxide in 68 cc. of water it dissolved completely in about ninety hours. Alcoholic potassium hydroxide or more concentrated aqueous solutions did not work as well. The acid was liberated by adding dilute sulfuric acid and extracting with ether. Yield: 5.4 g.; b. p., 165–168° (25 mm.). As little gas was given off during the distillation, one molecule of carbon dioxide had been split off during the long boiling. Pickard and Yates⁴ found the same in the case of phenylallylmalonic ester. In order to remove the phenylacetic acid present, the acid was boiled with water and barium carbonate, the aqueous solution of the very soluble barium salts filtered and treated with silver nitrate solution. The granular precipitate of silver salts was thoroughly washed with water to remove the fairly soluble silver phenylacetate. The salt of α -phenylisovalerianic acid is only slightly soluble.

Anal. Calcd. for $C_{11}H_{18}O_2Ag$: Ag, 37.9. Found: Ag, 38.1.

To obtain the free acid, 9.7 g. of silver salt was shaken with ether and 5 g. of nitric acid in 100 cc. of water; yield, 5.1 g.; b. p., 159–160° (14 mm.); m. p., 60°. The odor is similar to that of phenylacetic acid but more disagreeable and clinging. The acid prepared from the ketone as well as the synthetic β -acid does not have a pronounced odor.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.86. Found: C, 74.1; H, 7.89.

It was not found possible to obtain a solid nitro compound by heating with 75% nitric acid.

The anilide melted at 132–133°.

Anal. Calcd. for $C_{17}H_{19}ON$: C, 80.6; H, 7.5; N, 5.53. Found: C, 81.1; H, 7.7; N, 5.8.

β -Phenylisovalerianic Acid.—Dimethylphenylcarbinol was prepared by the action of methylmagnesium iodide on acetophenone and the hydroxyl substituted with chlorine by saturating with dry hydrogen chloride at 0°.⁵ These reactions worked smoothly. The crude chloride prepared in this manner from 18.6 g. of the carbinol was poured on ice, extracted with ether, washed with sodium bicarbonate solution and dried carefully with anhydrous sodium sulfate. The ethereal solution was then added to a solution of 3.2 g. of sodium and 22 g. of ethyl malonate in 35 g. of absolute alcohol. The clear $C_6H_5C(CH_3)_2Cl + NaCH(COOC_2H_5)_2 \longrightarrow C_6H_5C(CH_3)_2CH(COOC_2H_5)_2 \longrightarrow C_6H_5C(CH_3)_2CH_2COOH$

mixture gradually became cloudy and after twelve hours contained considerable precipitate. It was still slightly alkaline but became neutral after the ether and part of the alcohol had been distilled off. Water was added and the product extracted with ether. On distilling almost all came over up to 119°, 17 mm. Evidently the chief reaction is $C_6H_5CCl(CH_3)_2 + NaCH(COOC_2H_5)_2 \longrightarrow C_6H_5C(CH_3)=CH_2 + H_2C(COOC_2H_5)_2 + NaCl$

A small residue boiled at 150–180° (13 mm.); yield, 4.3 g. Without further purification it was boiled with 7.5 g. of potassium hydroxide in 14 cc. of water. The oil dissolved in two hours, with the exception of a few drops having a strong odor; these were distilled off with steam. The liquid was acidified with sulfuric acid and extracted twice with ether. After removing the ether, the residue was heated to 200° in an oil-

⁴ Pickard and Yates, *J. Chem. Soc.*, 95, 1015 (1909).

⁵ Klages, *Ber.*, 35, 2638 (1902).

bath and, after the foaming and evolution of gas had ceased, was distilled; yield, 1.58 g.; b. p., 163° (8 mm.), 167° (10 mm.); m. p., 57.5–58.5°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.86. Found: C, 73.9; H, 7.9.

Heated with 75% nitric acid a nitro compound was formed: m. p. 166–168° (not recrystallized). The anilide melted at 121–123°.

The following table gives the melting points and the mixed melting points of the various derivatives and shows the identity of the acid from the ketone with the synthetic beta acid.

TABLE I
PHYSICAL CONSTANTS

	Acid, m. p., °C.	Nitro deriv., m. p., °C.	Anilide, m. p., °C.
1 Acid from ketone	58–58.5	169–172	122–123
2 α -Acid	60	132–133
3 β -Acid	57.5–58.5	166–168	121–123
1 + 2	35–40	110–119
1 + 3	57.5–58.5	166–170	121–123

Summary

Mesityl oxide has been found to react with benzene in the presence of anhydrous aluminum chloride to give β -phenylisobutyl methyl ketone. Of the latter a semicarbazone, an oxime, a nitro and a tetrabromo derivative have been prepared. Treated with anhydrous zinc chloride the ketone yields a saturated, stable, crystalline hydrocarbon, $C_{24}H_{28}$, which gives a trinitro derivative. The ketone was reduced to the carbinol, from which an unsaturated hydrocarbon, $C_{12}H_{16}$, is produced by the action of zinc chloride. On oxidation with sodium hypobromite solution, the ketone gives a phenylisovaleric acid which is identical with one described by Eijkman as the α -phenyl acid. By the synthesis of both the α - and the β -phenylisovaleric acids by the malonic ester method, it is shown that the acid from the ketone is the β -acid. The true α -acid has not before been prepared.

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