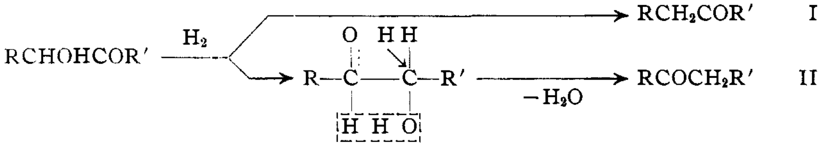
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Benzoin Reduction. II. The Mechanism of Ketone Formation. The Case of *m*-Chlorobenzanisoin

BY SANFORD S. JENKINS AND EDWIN M. RICHARDSON

It has been shown previously[1] that certain unsymmetrical benzoins produce *two isomeric* desoxybenzoins when reduced with tin and hydrochloric acid in alcoholic solution and the results obtained were explained by the equations

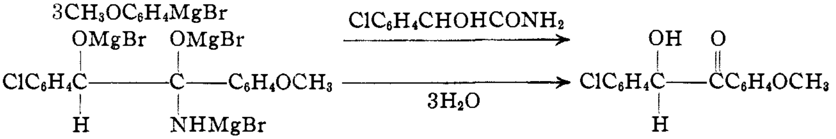


$$RCHOHCOR' \xrightarrow{H_2} RCH_2COR' \quad \text{I}$$

$$RCHOHCOR' \xrightarrow{H_2} R\text{—}\underset{H}{\overset{O}{C}}\text{—}\underset{OH}{\overset{HH}{C}}\text{—}R' \xrightarrow[-H_2O]{} RCOCH_2R' \quad \text{II}$$

This explanation was justified by the fact that the glycol when prepared independently and dehydrated, invariably produced the ketone corresponding to reaction II to the exclusion of I.

The object of the present article is to describe the results which were obtained in the reduction, under similar conditions, of *m*-chlorobenzanisoin in order to test further the validity of the above explanation. This benzoin, which has not been described previously, was prepared in the usual manner by condensing *m*-chlorobenzaldehyde and anisaldehyde in the presence of potassium cyanide. It was shown to be *m*-chloro-α-hydroxybenzyl *p*-methoxyphenyl ketone by comparison with this substance as obtained by reacting *m*-chloromandelamide[2] with *p*-methoxyphenylmagnesium bromide according to the equations



$$3CH_3OC_6H_4MgBr \xrightarrow{ClC_6H_4CHOHCONH_2} ClC_6H_4\underset{H}{\overset{OMgBr}{C}}\text{——}\underset{NHMgBr}{\overset{OMgBr}{C}}\text{—}C_6H_4OCH_3 \xrightarrow[3H_2O]{} ClC_6H_4\underset{H}{\overset{OH}{C}}\text{——}\overset{O}{\overset{\|}{C}}C_6H_4OCH_3$$

When oxidized with Fehling's solution the benzoin produced the benzil and when reduced with sodium amalgam *sym*-*m*-chloro-*p*′-methoxydiphenylethylene glycol was obtained. The glycol was dehydrated by heating with a solution consisting of 10% concd. sulfuric acid in glacial acetic acid and *p*-methoxybenzyl *m*-chlorophenyl ketone was isolated. The filtrate was carefully examined for the isomeric ketone but only intractable gum could be separated. That the ketone actually has the structure assigned was shown by comparison with the substance as obtained by condensing *p*-methoxyphenylacetamide with *m*-chlorophenylmagnesium iodide according to the reactions

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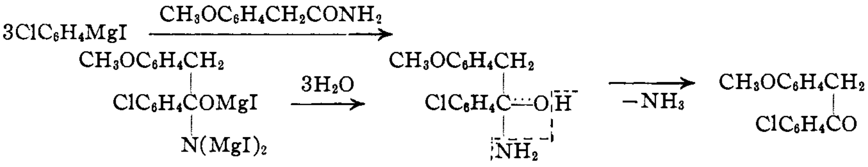
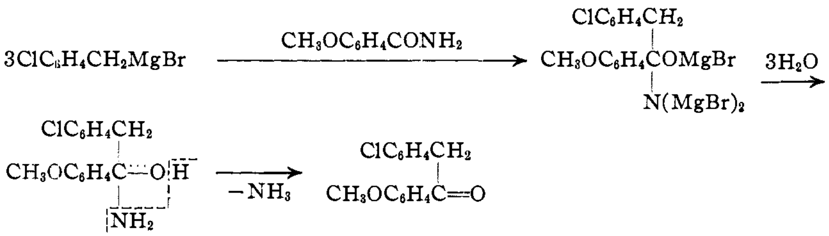
(1) Jenkins, THIS JOURNAL, **54**, 1153 (1932).

(2) Jenkins, *ibid.*, **53**, 2341 (1931).



$$3ClC_6H_4MgI \xrightarrow{CH_3OC_6H_4CH_2CONH_2} ClC_6H_4\overset{CH_3OC_6H_4CH_2}{\underset{N(MgI)_2}{C}}OMgI \xrightarrow{3H_2O} ClC_6H_4\overset{CH_3OC_6H_4CH_2}{\underset{NH_2}{C}}{-}OH \xrightarrow[-NH_3]{} ClC_6H_4\overset{CH_3OC_6H_4CH_2}{C}O$$

and also by converting it into the oxime, which was rearranged in the Beckmann manner[3] to *p*-methoxyphenylaceto-*m*-chloroanilide the structure of which was established by comparison with an authentic sample (see experimental part). The isomeric ketone, which is *m*-chlorobenzyl *p*-methoxyphenyl ketone, was also prepared independently by condensing *m*-chlorobenzyl bromide[4] with *p*-methoxybenzamide according to the method of synthesizing desoxybenzoins which has been described previously.[5] The reactions may be represented as



$$3ClC_6H_4CH_2MgBr \xrightarrow{CH_3OC_6H_4CONH_2} CH_3OC_6H_4\overset{ClC_6H_4CH_2}{\underset{N(MgBr)_2}{C}}OMgBr \xrightarrow{3H_2O} CH_3OC_6H_4\overset{ClC_6H_4CH_2}{\underset{NH_2}{C}}{-}OH \xrightarrow[-NH_3]{} CH_3OC_6H_4\overset{ClC_6H_4CH_2}{C}{=}O$$

The oxime of this ketone, when rearranged in the Beckmann manner, produced *m*-chlorophenylaceto-*p*-methoxyanilide. Assuming that a *cis* shift takes place between the groups, the oximes have the *anti* benzyl configuration.

The benzoin was reduced with tin and hydrochloric acid in alcoholic solution and both of the above ketones were found to be present in the reduction mixture. By careful fractional crystallization *p*-methoxybenzyl *m*-chlorophenyl ketone was obtained pure in about 10% yield. The major portion of the product, however, melted at 58–60° and proved to be a mixture of the two isomers as was shown by the fact that the melting point was raised when either ketone was added. A portion of the mixture was oximated and *m*-chlorobenzyl *p*-methoxyphenyl ketoxime was obtained by fractional crystallization in a yield of about 20%.

The evidence presented is thus conclusive proof that both isomeric desoxybenzoins are obtained in the reduction of this benzoin under the conditions of the experiment and is a further substantiation of the explanation of the mechanism of these reactions which was previously advanced.

Two other members of the series were prepared. Thus by condensing anisaldehyde with *m*-chlorobenzylmagnesium bromide *m*-chlorobenzyl-*p*-methoxyphenylcarbinol was obtained in a satisfactory yield. This carbinol

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[3] Jenkins, THIS JOURNAL, **55**, 703 (1933).

[4] Jenkins, *ibid.*, **55**, 2896 (1933).

[5] Jenkins and Richardson, *ibid.*, **55**, 1618 (1933).

could be easily dehydrated to form the corresponding stilbene, *sym-m*-chloro-*p*′-methoxydiphenylethylene.

It is our opinion that most, if not all, of the unsymmetrical benzoins, if reduced in the manner described here and in the preceding article, would be found to produce the two theoretically possible desoxy ketones. Although it is possible that reaction II might be very slow in comparison to I or that the glycol might even lose water to produce I, in every case so far studied both isomeric ketones have been obtained.

Experimental

Preparation of *m*-Chlorobenzanisoin

First Method.—To a solution of 13.60 g. of anisaldehyde, 14.00 g. of *m*-chlorobenzaldehyde and 70 cc. of alcohol was added 6.00 g. of potassium cyanide dissolved in 30 cc. of water. The mixture was refluxed on the water-bath for ninety minutes and placed in the refrigerator. After standing for twenty-four hours the crystalline material was separated, washed with water and recrystallized from slightly diluted alcohol. Yields of 25 to 30% were obtained. Recrystallized from a mixture of benzene and ligroin the substance was obtained as clusters of thick white prisms melting at 85.5° (corr.).

Second Method.—The Grignard reagent from 18.70 g. of *p*-bromoanisole and 2.50 g. of magnesium was prepared in the usual manner. After adding 4.64 g. of *m*-chloromandelamide[2] the solution was refluxed for twenty-five hours and then poured into 200 cc. of ice-cold 10% sulfuric acid. The mixture was stirred occasionally and allowed to stand at room temperature for two hours and then twice extracted with ether. The ether extract was steam distilled and the product was isolated as a yellow gum. After several crystallizations from dilute alcohol and then from benzene-ligroin the substance was obtained in a yield of about 20%, based on the amide used, as thick white prisms which proved to be identical with the compound prepared by method one.

***m*-Chlorobenzanisil.**—To a boiling alcoholic solution of the benzoin (water-bath) strong Fehling's solution was slowly added until an excess was present. After thirty minutes the hot solution was filtered and diluted with water. On standing the benzil separated and was recrystallized from dilute alcohol. The substance was obtained in a yield of about 50% as fine yellow needles which melted at 88° (corr.).

***sym-m*-Chloro-*p*′-methoxydiphenylethyleneglycol.**—This compound was obtained in a yield of about 60% by reducing the benzoin in alcoholic solution with 4% sodium amalgam at room temperature according to the method of preparing glycols which was described in article I.[1] The substance is soluble in alcohol and is best purified by recrystallization from a mixture of benzene and ligroin, from which it is obtained as white prisms melting at 101.5–102.5° (corr.).

Preparation of *p*-Methoxybenzyl *m*-Chlorophenyl Ketone

First Method.—Two grams of the glycol was dissolved in 20 cc. of glacial acetic acid containing 2.0 g. of concentrated sulfuric acid. The solution was refluxed for one hour in an apparatus with ground glass connections and then diluted with about 100 cc. of water. After standing for several hours the yellow solid was separated and recrystallized from dilute alcohol until pure. It consisted of colorless plates melting at 73–74° (corr.) and was obtained in a yield of about 25%. The mother liquors were carefully examined for the isomeric ketone but only gum-like material could be isolated.

Second Method.—A mixture of 5.00 g. of *m*-chlorobenzanisoin, 6.00 g. of mossy tin, 0.30 g. of copper sulfate, 30 cc. of concentrated hydrochloric and 50 cc. of alcohol was refluxed for seven hours and diluted with about 100 cc. of water. After standing for several hours the solid was separated. It weighed about 3.0 g. and melted at 55–65°. After several crystallizations from alcohol a fraction of about 0.60 g. consisting of colorless plates and melting at 73–74° was isolated. This substance proved to be identical with the ketone obtained in the dehydration of the glycol. The filtrates were combined and evaporated to about a third of the original volume and allowed to stand (continued below).

Third Method.—The Grignard reagent from 7.20 g. of *m*-chloroiodobenzene and 0.85 g. of magnesium was prepared in the usual manner. One and two-tenths grams of *p*-methoxyphenylacetamide was then added and the solution refluxed in an atmosphere of hydrogen for twenty-four hours. The ketone was obtained by means of the technique which has been described previously.[3] The yield in this case was not very good—about 20% based on the amide employed. The product proved to be identical in every respect with the substance obtained in methods one and two.

Almost quantitative yields of *p*-methoxyphenylacetamide are obtained by allowing a mixture of the methyl ester and concd. ammonium hydroxide to stand at room temperature for forty-eight hours. Practical purity is obtained by washing with ether; thin plates, m. p. 189–190° (corr.).

Preparation of *p*-Methoxybenzyl *m*-Chlorophenyl Ketoxime.—A mixture of 0.50 g. of the ketone prepared by either method, 0.50 g. of hydroxylamine hydrochloride, 0.80 g. of potassium acetate and 15 cc. alcohol was heated on the water-bath for three hours and diluted with enough hot water to dissolve the potassium chloride formed and cause a cloudiness. After standing in the refrigerator for several hours the solution deposited 0.45 g. of solid which after recrystallization from dilute alcohol consisted of white needles melting at 74–75° (corr.).

Rearrangement of *p*-Methoxybenzyl *m*-Chlorophenyl Ketoxime.—The oxime was rearranged with phosphorus pentachloride in absolute ether employing the technique described in a previous article.[5] The anilide thus obtained was compared (melting point and mixed melting point) with the two theoretically possible anilides, *viz.*, *p*-methoxyphenylacet-*m*-chloroanilide obtained by heating *p*-methoxyphenylacetic acid[6] with *m*-chloroaniline in an oil-bath at 180–190° for three hours and *m*-chlorobenzoyl-*p*-methoxybenzylamine, which was prepared in an analogous manner from *m*-chlorobenzoic acid and anisylamine.[7] The rearranged substance proved to be identical with the first anilide. This evidence thus establishes the structure of the ketone and indicates that the oxime has the *anti* benzyl configuration.

Preparation of *m*-Chlorobenzyl *p*-Methoxyphenol Ketone

First Method.—This ketone was prepared according to the Grignard method of obtaining desoxybenzoins recently described[5] by condensing *m*-chlorobenzylmagnesium bromide with *p*-methoxybenzamide. Four equivalents of the Grignard reagent to one equivalent of the amide were used and the mixture was heated for forty-eight hours. The ketone was obtained in a yield of 60% based on the amide employed. Recrystallized from alcohol it consists of white plates and melts at 70–71° (corr.).

Second Method.—The filtrate obtained in the second method of preparing *p*-methoxybenzyl *m*-chlorophenyl ketone (see above) on standing deposited about 2.0 g. of solid which after recrystallization from alcohol melted at 58–60° and proved to be a mixture of both ketones since when mixed with either the melting point was raised. Although the pure ketone could not be separated from this mixture after oximation the pure oxime was obtained (see below).

Preparation of *m*-Chlorobenzyl *p*-Methoxyphenyl Ketoxime.—This oxime was obtained from the Grignard ketone according to the general method[5] mentioned above in a

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(6) Mauthner, *Ann.*, **370**, 374 (1909).

(7) Goldschmidt and Polonowska, *Ber.*, **20**, 2407 (1887).

yield of 90% after crystallization from alcohol as white needles melting at 106.5–107.5° (corr.).

One gram of the mixture of ketones obtained in the reduction of the benzoin (see above) was oximated in a similar manner and after careful fractionation 0.22 g. of the pure oxime was obtained.

Rearrangement of *m*-Chlorobenzyl *p*-Methoxyphenyl Ketoxime.—The oxime was rearranged according to the method previously described[3] and the structure of the resulting anilide was established by comparison with the two theoretically possible anilides, *viz.*, *m*-chlorophenylacet-*p*-methoxyanilide obtained by heating *m*-chlorophenylacetic acid[4] and *p*-anisidine in an oil-bath for three hours at 170–190° and *p*-methoxybenzoyl-*m*-chlorobenzylamine prepared similarly from anisic acid and *m*-chlorobenzylamine.[8] The anilide obtained by rearrangement proved to be identical with the first synthetic product. The oxime thus has the *anti* benzyl configuration.

Preparation of *m*-Chlorobenzyl-*p*-methoxyphenylcarbinol.—The Grignard reagent of 0.10 mole of *m*-chlorobenzyl bromide and 2.50 g. of magnesium was prepared in the usual manner. To the solution 12.0 g. of anisaldehyde dissolved in 100 cc. of absolute ether was added. The mixture was heated and mechanically stirred for two hours and then poured into 200 cc. of ice-cold 10% ammonium chloride solution. After extraction with ether, drying with anhydrous sodium sulfate and evaporating the solvent *in vacuo* the carbinol was obtained as a yellow viscous oil in a yield of about 75%. Considerable

TABLE I

CONSTANTS AND ANALYTICAL DATA OF *m*-CHLOROBENZANISOIN AND DERIVATIVES

Compound	Appearance	M. p., °C. (corr.)	Mol. wt. (Rast) Calcd.	Found	Formula	Chlorine, % (Parr bomb) Calcd.	Found
Benzil	Fine yellow needles	88	274.5	263	$C_{15}H_{11}ClO_3$	12.91	13.01
Benzoin	Cream granules	85.5	276.5	287	$C_{15}H_{13}ClO_3$	12.81	12.96
Hydrobenzoin	White prisms	101.5–102.5	278.5	277	$C_{15}H_{15}ClO_3$	12.72	12.87
p-Methoxybenzyl-*m*-chlorophenyl ketone	White plates	73–74	260.5	241	$C_{15}H_{13}ClO_2$	13.60	13.68
m-Chlorobenzyl-*p*-methoxyphenyl ketone	White plates	70–71	260.5	263	$C_{15}H_{13}ClO_2$	13.60	13.92
m-Chlorobenzyl-*p*-methoxyphenyl carbinol	Thick white plates	42–43	262.5	285	$C_{15}H_{15}ClO_2$	13.50	13.30
Stilbene	Cream leaves	96	244.5	228	$C_{15}H_{13}ClO$	14.50	14.68

TABLE II

CONSTANTS AND ANALYTICAL DATA OF OXIMES AND ANILIDES

Phenyl ketoxime	Appearance	M. p., °C. (corr.)	Chlorine found, %
Anti-*p*-methoxybenzyl-*m*-chloro-	White needles	74–75	13.00
Anti-*m*-chlorobenzyl-*p*-methoxy-	White needles	106.5–107.5	13.09

Amide	Appearance	M. p., °C. (corr.)	Chlorine found, %
m-Chlorophenylacet-*p*-methoxyanilide	Long, thin plates	148.5	12.93
p-Methoxybenzoyl-*m*-chlorobenzylamine	Soft, white plates	161	12.89
p-Methoxyphenylacet-*m*-chloroanilide	Thin plates	86.5	12.85
m-Chlorobenzoyl-*p*-methoxybenzylamine	Colorless leaves	92.5	12.60

The oximes and amides all have the molecular formula $C_{15}H_{14}NClO_2$ and calculated chlorine content of 12.90%.

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(8) This amine was obtained by reducing *m*-chlorobenzaldoxime with zinc and acetic acid according to the method of Franzen [*Ber.*, **38**, 1415 (1905)] for preparing the *o*-chloro isomer. The procedure was shortened, however, by steam distilling the crude amine rather than separating it as the carbonate; colorless oil, b. p. 105–110° (13 mm.). See also Braun, Kühn and Weismantel [*Ann.*, **449**, 273 (1926)] for a catalytic method of preparation.

difficulty was experienced in inducing the substance to crystallize. Success was attained, however, by dissolving it in a warm mixture of benzene and ligroin and seeding with a few crystals which were obtained by allowing a little of the solution to remain on a watch glass at room temperature for several days. The substance was obtained as thick, white plates melting at 43–44° (corr.).

Preparation of *sym-m*-Chloro-*p*'-methoxydiphenylethylene.—This stilbene was obtained in 60% yield by heating for thirty minutes the above carbinol with twenty parts of a solution consisting of 20% concentrated hydrochloric acid in glacial acetic acid. The crude material was isolated by diluting the solution with water. Recrystallized from alcohol the substance was obtained as cream colored leaves melting at 96° (corr.).

Summary

The explanation of the mechanism of the reduction of unsymmetrical benzoins which was previously advanced has been substantiated in the present work.

m-Chlorobenzanisoin, which has not been described previously, is shown to be *m*-chloro-α-hydroxybenzyl *p*-methoxyphenyl ketone by an independent synthesis.

When reduced under suitable conditions this benzoin was found to produce *m*-chlorobenzyl *p*-methoxyphenyl and *p*-methoxybenzyl *m*-chlorophenyl ketones, the structures of which were established. In the course of this work thirteen new compounds were prepared and characterized.

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Some Mono and Dibromo Derivatives of Meta Cresol. II

BY RALPH C. HUSTON AND WALTER J. PETERSON

In a recent report[1] from this Laboratory several new bromo derivatives of *m*-cresol were prepared and their structures conclusively proved. A continuation of this work has resulted in the preparation of several new derivatives. Two new methods for the protection of positions during bromination have been developed.

6-Bromo-*m*-cresols

From 6-Amino-*m*-cresols.—Pure *m*-cresol was nitrated according to the method of Staedel and Kolb,[2] and the isomeric products separated by steam. The volatile 6-nitro product (m. p. 56°) was converted to the 6-amino hydrochloride by reduction in alcohol with stannous chloride and hydrochloric acid.[3] Attempts to change the hydrochloride (m. p. 212°) to the free base were unsuccessful. The free amine (m. p. 157°) may be obtained by reduction of the nitro compound in accordance with the method of Hodgson and Beard.[4] 6-Nitro-*m*-cresol (33 g.) was treated with 400 cc. of water containing

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[1] Huston and Hutchinson, THIS JOURNAL, **54**, 1504 (1932).

[2] Staedel and Kolb, *Ann. Chem.*, **259**, 210 (1890).

[3] (a) Raiford and Leavell, THIS JOURNAL, **36**, 1505 (1914); (b) Raiford, *Am. Chem. J.*, **46**, 419 (1911).

[4] Hodgson and Beard, *J. Chem. Soc.*, **127**, 498 (1925).