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

The Grignard Reaction in the Synthesis of Ketones. V. The Preparation of the Isomeric *p*-Chlorobenzanisoins

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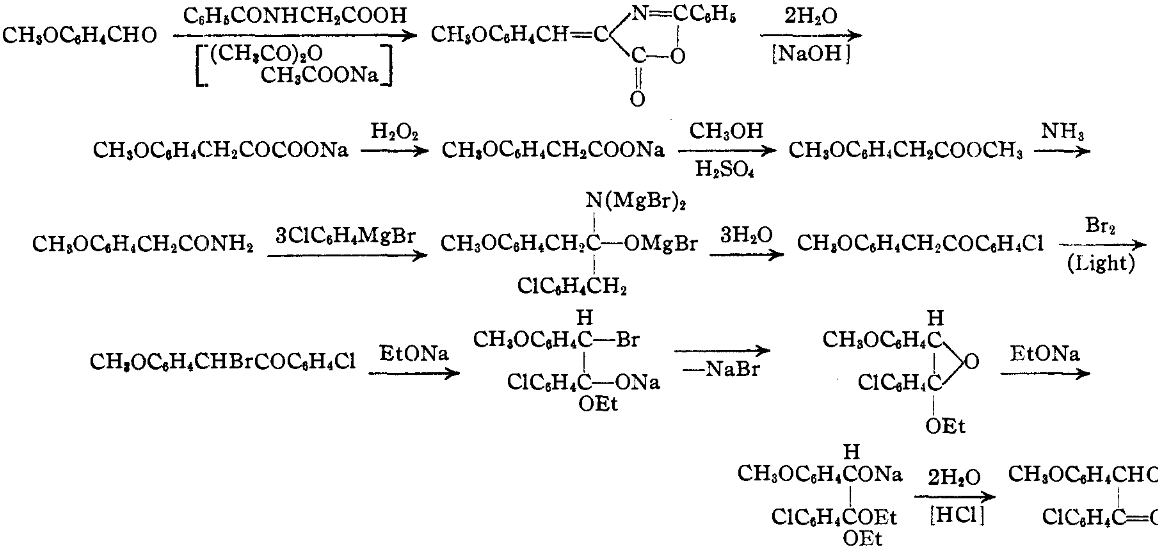
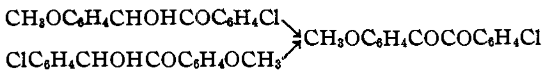
The object of the present article is to describe the synthesis of the isomeric *p*-chlorobenzanisoins. This work was carried out in order to further test the applicability of the method of preparing unsymmetrical benzoins described in the previous article[1] and to obtain starting material for another research the nature of which has been recently mentioned.[2]

One of the isomers, α-hydroxy-*p*-methoxybenzyl *p*′-chlorophenyl ketone, was prepared by the following reactions



The other, which is α-hydroxy-*p*-chlorobenzyl *p*′-methoxyphenyl ketone, was obtained from *p*-chlorobenzyl *p*′-methoxyphenyl ketone in a similar manner.

The non-identity of the substances was shown by the difference of their melting points and the depression of the melting point of a mixture. That they are actually isomers was shown by the fact that the same benzil was obtained when either of them was oxidized with Fehling's solution.



The structure of *p*-methoxybenzyl *p*′-chlorophenyl ketone was confirmed by converting it into the oxime which was rearranged in the Beckmann manner to *p*-methoxyphenylacet-*p*′-chloranilide.

Experimental Part

Preparation of *p*-Methoxyphenylacetamide.—Methyl *p*-methoxyphenylacetate, prepared from anisaldehyde by means of the method of Cain, Simonsen and Smith,[3] was allowed to stand at room temperature with concd. ammonium hydroxide for forty-eight hours. The amide was obtained in a yield of 30% based on the aldehyde employed and melted at 189.5–190.5° (corr.).

Preparation of *p*-Methoxybenzyl *p*′-Chlorophenyl Ketone.—The Grignard reagent from 38.30 g. of *p*-chlorobromobenzene and 5.00 g. of magnesium turnings was first made and to this was added 11.00 g. of *p*-methoxyphenylacetamide. After refluxing the mixture for thirty-six hours the ketone was isolated in the usual manner (see previous papers). Recrystallized from ligroin it was obtained in a yield of 23% as thin, colorless plates which melted at 111° (corr.).

Preparation of *p*-Chlorobenzyl *p*′-Methoxyphenyl Ketone.—This ketone[4] was prepared in a yield of 71% by condensing *p*-methoxybenzamide with *p*-chlorobenzylmagnesium bromide.

Preparation of the α-Bromo Derivatives.—These derivatives were prepared in the manner described in the preceding article[1] by treating 0.01 mole of each of the above ketones dissolved in warm carbon tetrachloride with the theoretical amount of bromine in the presence of a 500-watt tungsten lamp. The substances were purified by recrystallization from ligroin.

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(1) Jenkins, THIS JOURNAL, **56**, 682 (1934).

(2) Jenkins, *ibid.*, **55**, 3048 (1933).

(3) Cain, Simonsen and Smith, *J. Chem. Soc.*, **103**, 1035 (1913).

(4) Jenkins, THIS JOURNAL, **55**, 703 (1933).

α-Bromo-*p*-methoxybenzyl *p*′-chlorophenyl ketone separated in clusters of fine white needles in a yield of 83% melting at 85.5–86° (corr.). The isomer, α-bromo-*p*-chlorobenzyl *p*′-methoxyphenyl ketone, was obtained in a yield of 85% as short, white needles melting at 106.5° (corr.).

Preparation of the Isomeric *p*-Chlorobenzanisoins.—These substances were prepared by the method previously described[1] from the bromo derivatives.

α-Hydroxy-*p*-methoxybenzyl *p*′-chlorophenyl ketone was obtained in a yield of 70% from ligroin, as clusters of fine, white needles melting at 70.5–71.5° (corr.). The isomeric benzoin was obtained in similar manner in a yield of 85% as thick cream-colored needles which melted at 84.5–85.5° (corr.).

Preparation of *p*-Chloro-*p*′-methoxybenzil.—To 0.20 g. of each of the above benzoins dissolved in alcohol and heated on the hot-plate was added an excess of Fehling's solution. When oxidation was complete the solutions were filtered hot, diluted with water and allowed to crystallize. The benzil was prepared in yields of about 60% from either benzoin as long, thin, lemon-yellow crystals melting at 129.5° (corr.).

Preparation of *p*-Methoxybenzyl *p*′-Chlorophenyl Ketoxime.—This oxime was prepared according to the general method[4] described previously, in a yield of 90% after crystallization from benzene–ligroin solution as stout cream-colored needles melting at 87.5–88° (corr.).

Preparation of *p*-Methoxyphenylacet-*p*-chloranilide

Rearrangement of Oxime.—A solution of 0.50 g. of the oxime in absolute ether was treated with about 1.0 g. of phosphorus pentachloride. The cooled mixture was shaken, allowed to stand for ten minutes and then poured into ice water. After driving off the ether with a stream of air the solid was separated and recrystallized from dilute alcohol. It was obtained as thin, white plates and melted at 138° (corr.).

Synthesis from Acid and Amine.—A mixture of 0.01 mole each of *p*-methoxyphenylacetic acid and *p*-chloroaniline was heated for three hours in an oil-bath at 180–190°. The anilide was purified by crystallization from dilute alcohol and was identical with the amide from the rearrangement.

TABLE I

ANALYTICAL DATA

Compounds	Mol. wts. (Rast) Calcd.	Found	Chlorine (Parr bomb) Calcd.	Found
p-Methoxybenzyl *p*′-chlorophenyl ketone	260.56	252	13.60	13.48
			Bromine	
α-Bromo-*p*-methoxybenzyl *p*′-chlorophenyl ketone	339.46	325	23.54	23.37
α-Bromo-*p*-chlorobenzyl *p*′-methoxyphenyl ketone	339.46	332	23.54	23.74
			Chlorine	
α-Hydroxy-*p*-methoxybenzyl *p*′-chlorophenyl ketone	276.56	270	12.82	12.73
α-Hydroxy-*p*-chlorobenzyl *p*′-methoxyphenyl ketone	276.56	273	12.82	12.68
p-Methoxy-*p*-chlorobenzil	274.54	280	12.91	12.80
p-Methoxybenzyl *p*′-chlorophenyl ketoxime			12.86	12.98
p-Methoxyphenylacet-*p*′-chloranilide			12.86	12.66

Summary

The method of preparing isomeric unsymmetrical benzoins from desoxybenzoins which was previously described has been extended to the synthesis of α-hydroxy-*p*-methoxybenzyl *p*′-chlorophenyl and α-hydroxy-*p*-chlorobenzyl *p*′-methoxyphenyl ketones. When oxidized each of these benzoins produced *p*-methoxy-*p*′-chlorobenzil.

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