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

The Grignard Reaction in the Synthesis of Ketones. II. The Preparation of a Series of Mono- and Di-chlorodesoxybenzoins

BY SANFORD S. JENKINS AND EDWIN M. RICHARDSON

In the preceding article[1] a new method of synthesizing desoxybenzoins (benzylphenyl ketones) by means of the Grignard reaction was described. It was found that these compounds could be prepared by the reaction of benzylmagnesium halides with primary benzamides and that quite satisfactory yields were obtained when the reactants, in the ratio of three to four equivalents of the former to one of the latter, were heated over sufficiently long periods of time. Although rearrangements are known to take place when benzylmagnesium halides are treated with certain substances,[2] no evidence of any abnormal product was obtained in this work. By means of the Beckmann reaction[1] the oximated derivatives were transformed into the corresponding anilides, the structures of which were established by comparison with authentic specimens.

In the present article eight mono- and di-chlorodesoxybenzoins, which were prepared and shown to be authentic by the methods outlined above, will be described. Thus by condensing *o*-chlorobenzamide and benzamide with benzylmagnesium chloride and *o*-chlorobenzylmagnesium bromide, benzyl *o*-chlorophenyl, *o*-chlorobenzyl phenyl and *o*-chlorobenzyl *o*-chlorophenyl ketones were prepared. In a similar manner benzyl *p*-chlorophenyl,[3] *p*-chlorobenzyl phenyl[4] and *p*-chlorobenzyl *p*-chlorophenyl ketones were obtained from the corresponding amides and Grignard reagents. Finally *o*- and *p*-chlorobenzamides were treated with *o*- and *p*-chlorobenzylmagnesium bromides to produce *o*-chlorobenzyl *p*-chlorophenyl and *p*-chlorobenzyl *o*-chlorophenyl ketones (see Table I for preparational data and constants of the ketones).

Under the conditions of our experiments seven of the ketones produced single oximes which proved to be of the *anti*-benzyl types. From *o*-chlorobenzyl *o*-chlorophenyl ketone, however, both the *syn*- and *anti*-benzyl ketoximes were obtained. It is quite possible that *syn* types could be prepared from the other ketones as well by suitably varying the conditions. In a later communication we shall describe the results of an extensive investigation dealing with the oximation of desoxy ketones in

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

[2] For references see Austin and Johnson, *ibid.*, **54**, 647 (1932); Gilman and Kirby, *ibid.*, **54**, 345 (1932).

[3] Benzyl *p*-chlorophenyl ketone, which was prepared by means of the Friedel–Crafts reaction, and the corresponding oxime have been described by Szego and Ostinelli [*Atti III congresso naz- chim. pura applicata*, p. 395–401 (1930); *cf. C. A.*, **25**, 1524 (1931)]. The compounds, if authentic, were impure, for the melting points given were over 5° too low.

[4] Petrenko-Kritschenko [*Ber.*, **25**, 2239 (1892)] has described the preparation of *p*-chlorobenzyl phenyl ketone but the melting point given was too low.

TABLE I

PREPARATIONAL DATA AND CONSTANTS OF KETONES WITH ANALYSES AND MOLECULAR WEIGHTS

Grignard	Benzamide	Time, hours	Letter	Ketone	Yield, %	Appearance	M. p., (corr.), °C.	Formula	Chlorine, %		Mol. wt.	
									Calcd.	Found	Calcd.	Found
$C_6H_5CH_2MgCl$	o-$ClC_6H_4CONH_2$	70	A	Benzyl o-chloro phenyl	71	Faint yellow oil	B. p. 176–178 (5 mm.)	$C_{14}H_{11}ClO$	15.37	14.85	230.5	241
o-$ClC_6H_4CH_2MgBr$	$C_6H_5CONH_2$	24	B	o-Chlorobenzyl phenyl	73	Clusters of cream colored needles	70.5	$C_{14}H_{11}ClO$	15.37	15.44	230.5	237
o-$ClC_6H_4CH_2MgBr$	o-$ClC_6H_4CONH_2$	50	C	o-Chlorobenzyl o-chlorophenyl	70	Faint yellow viscous oil	B. p. 195–210 (6 mm.)	$C_{14}H_{10}Cl_2O$	26.76	25.80	265	274
$C_6H_5CH_2MgCl$	p-$ClC_6H_4CONH_2$	14	D	Benzyl p-chloro phenyl	77	Cream colored scales	107.5	$C_{14}H_{11}ClO$	15.37	15.41	230.5	222
p-$ClC_6H_4CH_2MgBr$	$C_6H_5CONH_2$	24	E	p-Chlorobenzyl phenyl	70	Thin colorless plates	138	$C_{14}H_{11}ClO$	15.37	15.23	230.5	240
p-$ClC_6H_4CH_2MgBr$	p-$ClC_6H_4CONH_2$	24	F	p-Chlorobenzyl p-chlorophenyl	74	White needles	114	$C_{14}H_{10}Cl_2O$	26.76	26.86	265	275
o-$ClC_6H_4CH_2MgBr$	p-$ClC_6H_4CONH_2$	65	G	o-Chlorobenzyl p-chlorophenyl	80	Colorless needles	108.5	$C_{14}H_{10}Cl_2O$	26.76	26.69	265	270
p-$ClC_6H_4CH_2MgBr$	o-$ClC_6H_4CONH_2$	40	H	p-Chlorobenzyl o-chlorophenyl	72	White glittering scales	65	$C_{14}H_{10}Cl_2O$	26.76	26.87	265	275

TABLE II

CONSTANTS OF OXIMES AND ANILIDES WITH ANALYTICAL DATA

Letter	Ketoxime	Appearance	M. p. (corr.), °C.	Anilide	Appearance	M. p. (corr.), °C.	Oxime formula	Chlorine, %		Anilide formula	Chlorine, %	
								Calcd.	Found		Calcd.	Found
A	*Anti*-Benzyl o-chlorophenyl	White prisms	131.5–132.5	Phenylacet-o-chloro-	Fine white matted needles	120	$C_{14}H_{12}NClO$	14.46	14.52	$C_{14}H_{12}NClO$	14.46	14.28
B	*Anti*-o-Chlorobenzylphenyl	White prisms	85–86	o-Chlorophenylacet-	Clusters of fine white needles	140	$C_{14}H_{12}NClO$	14.46	14.38	$C_{14}H_{12}NClO$(5)		
C^1	*Anti*-o-Chlorobenzyl o-chlorophenyl	Balls of cream needles	103–104	o-Chlorophenylacet-o-chloro-	Fine white needles	159.5	$C_{14}H_{11}NCl_2O$	25.30	25.40	$C_{14}H_{11}NCl_2O$	25.30	2
C^2	*Syn*-o-Chlorobenzyl o-chlorophenyl	Colorless diamond-shaped plates	145–146	o-Chloro-benzoyl-o-chlorobenzylamine	White needles	111	$C_{14}H_{11}NCl_2O$	25.30	25.43	$C_{14}H_{11}NCl_2O$	25.30	25.40
D	*Anti*-Benzyl p-chlorophenyl	Long colorless glittering needles	122.5–123.5	Phenylacet-p-chloro-	Long thin colorless needles	168	$C_{14}H_{12}NClO$	14.46	14.52	$C_{14}H_{12}NClO$	14.46	14.31
E	*Anti*-p-Chlorobenzyl phenyl	White prisms	95–96	p-Chlorophenylacet-	Colorless prisms	168	$C_{14}H_{12}NClO$	14.46	14.67	$C_{14}H_{12}NClO$(5)		
F	*Anti*-p-Chlorobenzyl p-chlorophenyl	Short white needles	124.5–125.5	p-Chloro phenylacet-p-chloro-	Short white needles	190	$C_{14}H_{11}NCl_2O$	25.30	25.20	$C_{14}H_{11}NCl_2O$	25.30	25.08
G	*Anti*-o-Chlorobenzyl p-chlorophenyl	White prisms	105–106	o-Chlorophenylacet-p-chloro-	Cluster of fine hair-like needles	184	$C_{14}H_{11}NCl_2O$	25.30	25.18	$C_{14}H_{11}NCl_2O$	25.30	25.21
H	*Anti*-p-Chlorobenzyl o-chlorophenyl	Thick white prisms	88–89	p-Chlorophenylacet-o-chloro-	White prisms	171	$C_{14}H_{11}NCl_2O$	25.30	25.15	$C_{14}H_{11}NCl_2O$	25.30	25.40

which certain generalizations will be discussed. For the present, however, we are concerned with this study only as a means of further confirming the structures of the ketones (see Table II).

Experimental

The amides were prepared by refluxing the corresponding acids on the water-bath with double the calculated amount of thionyl chloride until the evolution of hydrogen chloride and sulfur dioxide ceased. The excess of thionyl chloride was then distilled under reduced pressure and the crude acid chlorides poured into ice-cold ammonium hydroxide solution. The resulting amides were purified by crystallization from water. The method is convenient and the yields are satisfactory.

The Grignard reagents were prepared and the condensations carried out according to the method and technique described in article I[1] of this series. In the present work it was found, however, that the yields could be improved and better products (not so yellow) obtained when the condensations were carried out in an atmosphere of hydrogen. Employing this modification the yield of ketone H was increased from 55 to 72%. The yields reported were obtained by treating four equivalents of the Grignard reagents (0.10 to 0.20 mole) to one equivalent (0.025 to 0.050 mole) of the amides. The yields were calculated on the basis of the amides employed and represent the product obtained after one crystallization from alcohol. The melting points of the once crystallized ketones were within two or at most four degrees of the fusing points (see Table I) of the pure compounds.

Ketone B was purified by recrystallization from ligroin (Skellysolve "C"), while D, E, F, G and H were recrystallized from alcohol.

The anilides, as obtained by rearrangement of the oximes, were obtained in yields of 55 to 80%. The structures of these substances were established by mixed melting points with authentic anilides prepared from the corresponding acids and amines.

The oximes listed were all prepared by mixing 1.00 g. of ketone, 1.00 g. of hydroxylamine hydrochloride, 1.60 g. of potassium acetate (dried) and 30 cc. of 95% alcohol. The mixture was allowed to stand overnight and heated on the water-bath under reflux for three hours. To the solution hot water was then added until the potassium chloride dissolved and a faint opalescence appeared. On slowly cooling the oximes usually crystallized without difficulty.

The crude oximes were obtained in yields of 90–99%. Oximes A and F were recrystallized from dilute alcohol (about 80%), while B, D, E, G and H were purified by recrystallization from ligroin (Skellysolve "C"). In order to separate C^1 and C^2 the following method (which may not be the best) was used: the mixture of crude oximes was dissolved in the smallest amount of slightly diluted (about 90%) alcohol and allowed to stand for several days at room temperature. When crystallization appeared to be complete, the oxime was separated and further purified in the same manner. By this means C^2 (*syn*-benzyl isomer) was obtained. The mother liquors were combined and evaporated to dryness under reduced pressure. The solid was then recrystallized from ligroin. This product (C^1) proved to be the *anti*-benzyl isomer. We are not certain that either of these isomers is entirely pure but each of them was recrystallized until its melting point remained constant. The relative yields of *syn* and *anti* isomers seemed to vary with different batches of the crude mixture although the *anti* isomer was always obtained in the greatest percentage.

The oximes were rearranged in the following manner: 0.50 g. of oxime was dissolved in 20 cc. of anhydrous ether and after cooling in an ice-bath the solution was treated with 1.0 g. of powdered phosphorus pentachloride. The mixture was then shaken for five minutes and poured into about 100 cc. of ice water. The ether was evaporated by means of a stream of air, after which the crude anilide was filtered, washed with water and crystallized from alcohol. In the case of oxime C^2 the purest anilide was obtained when the ether solution was refluxed on the water-bath for ten minutes.

For comparison the anilides were prepared independently by heating 0.010 mole weights of the corresponding acids and amines in an oil-bath at 180–200° for two hours. The anilides were crystallized from alcohol until pure. Anilides B and E have been described heretofore.[5]

o- and *p*-chlorophenylacetic acids were prepared according to the method of Mehner.[5] The nitriles, however, were not purified but were hydrolyzed directly to the acids by refluxing with concentrated hydrochloric acid for four hours.

The *o*-chlorobenzylamine employed in this work was obtained from *o*-chlorobenzaldoxime according to the method of Franzen.[6] The procedure was considerably shortened, however, by steam distilling the crude amine rather than separating it from the ether solution as the carbonate. The chloroanilines and chlorobenzyl halides employed in this work were purchased from the Eastman Kodak Company.

The molecular weight determinations of B, D, E, F, G and H were made by means of the Rast method[7] using borneol instead of camphor. The Menzies–Wright boiling point method[8] was employed in cases A and C.

The halogen analyses were made by the Parr bomb method.

Ketones A and C were not pure as is evidenced by their analyses. Because of the small quantities available (about 8 cc. of each) it was not feasible to purify them further.

Summary

The Grignard method of synthesizing desoxybenzoins, which was described in article I, has been extended.

By condensing primary benzamides with benzylmagnesium halides under suitable conditions a series of eight mono- and di- chloro ketones has been prepared and studied.

In no case was any evidence of an abnormal product observed in this type of Grignard reaction.

Under the conditions of the experiments seven of the ketones produced only *anti*-benzyl oximes. From *o*-chlorobenzyl *o*-chlorophenyl ketone both *syn*- and *anti*-benzyl ketoximes were obtained.

The oximes were rearranged by the Beckmann method and the structures of the resulting anilides were established.

In the course of this work twenty-one new compounds were obtained and characterized.

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(5) Mehner, *J. prakt. Chem.*, **62**, 562 (1900).

(6) Franzen, *Ber.*, **38**, 1415 (1905).

(7) Rast, *ibid.*, **B55**, 1051 (1922).

(8) Menzies and Wright, THIS JOURNAL, **43**, 2314 (1921).