

Dakin.<sup>5</sup> Four recrystallizations from alcohol gave 13.5 g. of pure levo  $\beta$ -phenyl-*n*-propylamine neutral *d*-malate and 4 g. more was obtained from the mother liquors; m. p. 182–184°;  $[\alpha]^{25D} -21.9^\circ$  (*c*, 4; water).

The resolution of the  $\beta$ -phenyl-*n*-propylamine by the tartrate salt was very slow. The salt, prepared by mixing the *dl*-amine with *d*-tartaric acid in mole proportions of 1:1, was recrystallized from alcohol twenty-three times, the last three recrystallizations changing the specific rotation from 31.2° to 31.7° (*c*, 4; water). The yield of the recovered amine was 10–15%; b. p. 102° (20 mm.);  $[\alpha]^{25D} 35.4^\circ$  (*c*, 2; absolute alcohol).

*Anal.* Calcd. for C<sub>9</sub>H<sub>13</sub>N: neut. eq., 135.1. Found: neut. eq. with methyl red, 138.3.

The salt prepared by treating the *dl*-amine with *d*-camphoric acid in mole proportions of 1:1 was recrystallized eighteen times from a mixture of equal parts of alcohol and ethyl acetate, the last three recrystallizations changing the specific rotation from –12.6 to –12.9° (*c*, 3.2; water). This salt contained the levo form of the amine.

Resolution with camphorsulfonic acid and menthoxyacetic acid was also extremely slow in ethyl acetate.

**Resolution of N-Methyl- $\beta$ -phenyl-*n*-propylamine.**—This compound was much more difficult to resolve than the previous, unmethylated one. The malate did not crystallize. N-Alkylation lowers the melting points of the salts of an amine and often makes resolution more difficult.

Seventy-six grams of N-methyl- $\beta$ -phenyl-*n*-propylamine, supplied by the Wm. S. Merrell Co., and 118 g. of *d*-camphorsulfonic acid were dissolved in 1200 ml. of ethyl acetate. After cooling in ice for several hours, 65 g. of salt was filtered off. This was recrystallized by dissolving in about 0.8 its weight of absolute alcohol, carefully adding 5–6 volumes of ether, and allowing to stand in ice for a short time. After 6 recrystallizations, 11 g. of pure dextro N-methyl- $\beta$ -phenyl-*n*-propylamine *d*-camphorsulfonate

(5) Dakin, *J. Biol. Chem.*, **59**, 7 (1924).

was obtained; m. p. 118–19°;  $[\alpha]^{25D} 28.8^\circ$  (*c*, 4; water). By working up the recrystallization liquors, 8.3 g. more was obtained; total yield, 19.3 g. or 20%.

The amine was recovered from 18.3 g. of the salt by liberating it with sodium hydroxide, extracting with ether, drying and distilling. The yield was 7 g., a 92% recovery; b. p. 103° (21 mm.);  $[\alpha]^{25D} 32.2^\circ$  (*c*, 2; absolute alcohol).

*Anal.* Calcd. for C<sub>10</sub>H<sub>15</sub>N: neut. eq., 149.14. Found: neut. eq., 150.0.

The levo form was obtained with *d*-mandelic acid. Thirty-eight grams of N-methyl- $\beta$ -phenyl-*n*-propylamine recovered from the mother liquors of the above resolution reacted with 38 g. of *d*-mandelic acid in 30 ml. of absolute alcohol. The salt was precipitated with 200 ml. of ether. In subsequent recrystallizations, the salt was dissolved in about 0.5 its weight of absolute alcohol and ether equal to 9–10 times the volume of alcohol used was added. The clear, supersaturated solution was allowed to stand in ice for a short time while crystallization took place. After 12 recrystallizations, 8.5 g. of pure levo N-methyl- $\beta$ -phenyl-*n*-propylamine *d*-mandelate was obtained; m. p. 86–7°;  $[\alpha]^{25D} 39.8^\circ$  (*c*, 7; water). From the mother liquors 4.5 g. more was obtained; total, 13 g.

The levo amine was recovered from 15.4 g. of the salt in the manner employed for the dextro form. The yield was 7 g., a 92% recovery; b. p. 101–102° (19 mm.);  $[\alpha]^{25D} -31.7^\circ$  (*c*, 2; absolute alcohol).

### Summary

1.  $\beta$ -Phenyl-*n*-propylamine has been completely resolved with *l*- and *d*-malic acids.
2. Both antipodes of N-methyl- $\beta$ -phenyl-*n*-propylamine have been obtained by resolution with *d*-camphorsulfonic acid and *d*-mandelic acid.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

## The Reaction of the Grignard Reagent with Esters of Highly Hindered Acids

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Failure to obtain tertiary carbinols from benzoylmesitylene and Grignard reagents<sup>1</sup> does not necessarily preclude the possibility of preparing them from mesitoic esters and the Grignard reagent. Morton and Peakes<sup>2</sup> found, in fact, that 2,4,6-tribromotriphenylcarbinol was formed by the action of phenylmagnesium bromide on methyl 2,4,6-tribromobenzoate but could not be made by the action of this reagent on 2,4,6-tribromobenzophenone. Whereas the carbonyl

group of esters is less reactive than that of ketones, it seemed that in highly hindered molecules this difference might be outweighed by the small size of the OR group as compared to that of the phenyl radical.

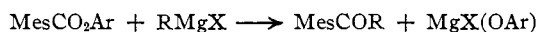
As a test of this possibility certain alkyl and aryl esters of mesitoic acid have been prepared and treated with the Grignard reagent. Evidence of reaction was obtained in all cases. Alkyl mesitoates when treated with alkylmagnesium halides yield mesitoic acid and the alkyl halide formed from the alkyl group of the ester and the halogen

(1) Fuson, Armstrong and Speck, *J. Org. Chem.*, **7**, in press (1942).

(2) Morton and Peakes, *THIS JOURNAL*, **58**, 2110 (1933).

atom of the reagent. No alkylation was observed in any of these reactions.<sup>3</sup>

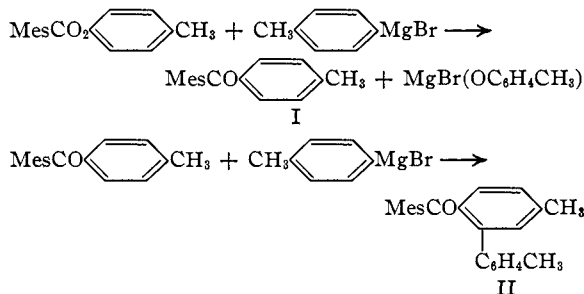
Aryl mesitoates reacted with the Grignard reagent in an entirely different manner. When alkylmagnesium halides were used, the ester was converted into the corresponding alkyl mesityl ketone and the phenol derived from the aryl radical that is removed.



In this way high yields of aceto- and propio-mesitylene were obtained from *p*-tolyl mesitoate and methyl- and ethylmagnesium halides, respectively. *p*-Cresol was formed also in each instance.

In a similar manner *p*-tolyl 2,4,6-triisopropylbenzoate reacted with methyl- and ethylmagnesium halides to yield, respectively, 2,4,6-triisopropylacetophenone and 2,4,6-triisopropylpropiophenone.

The products obtained by the action of arylmagnesium halides on aryl mesitoates were more complex but the first step in each case appeared to be the formation of the ketone. Thus, *p*-tolylmagnesium bromide reacted with *p*-tolyl mesitoate to yield *p*-cresol and 2-*p*-tolyl-4-methylbenzoylmesitylene (II). This result is to be explained by assuming that the ketone (I) is formed first just as with the alkylmagnesium halides. It has been shown<sup>1</sup> that ketones of this type may react with Grignard reagents in such a manner as to suffer arylation in an *ortho*-position. For example, when *p*-tolylmesitylene (I) was treated with *p*-tolylmagnesium bromide the tolylated ketone (II) was found among the products.



Similar results were obtained in the condensation of phenyl- and  $\alpha$ -naphthylmagnesium bromide with *p*-tolyl mesitoate. In addition, the action of *o*-methoxyphenylmagnesium bromide on *p*-tolyl mesitoate gave rise to *o*-(*o*-methoxyphenyl)-benzoylmesitylene, and *o*-(*m*-methoxyphenyl)-benzoylmesitylene was produced from *p*-tolyl mesito-

ate and *m*-methoxyphenylmagnesium bromide. It was obvious that arylation could be prevented by the use of mesitylmagnesium bromide. This experiment did indeed yield a small amount of dimesityl ketone. Curiously, the ketone was accompanied by a trace of mesitol. The formation of the latter has not been explained.

## Experimental

**Esters.**—The esters studied in this work were prepared by the condensation of the corresponding acid chloride and alcohol or phenol.

**Benzyl Mesitoate.**—One hundred and fifty-nine grams of mesitoyl chloride<sup>4</sup> was added slowly to 140 g. of benzyl alcohol, with stirring. After the addition was complete the mixture was heated for an hour, allowed to cool and poured into water, acidified with sulfuric acid. The ester was extracted with ether. The ether solution was washed with potassium bicarbonate solution, then with water and dried with sodium sulfate. The solvent was removed and the residue distilled under reduced pressure. The yield was 193 g. of benzyl mesitoate boiling at 164–169° (2.5 mm.); m. p. 38–39° (cor.).

*Anal.* Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>2</sub>: C, 80.28; H, 7.13. Found: C, 80.41; H, 7.35.

*n*-Butyl mesitoate was prepared in the same manner; b. p. 119–121° (3 mm.); *d*<sub>4</sub><sup>20</sup> 0.9839; *n*<sub>D</sub><sup>20</sup> 1.4920.

***p*-Tolyl Mesitoate.**—Thirty-three and one-half grams of mesitoyl chloride was added slowly to 20 g. of *p*-cresol. The solution was warmed until the evolution of hydrogen chloride ceased. The reaction mixture was dissolved in ethyl ether and the solution washed with three portions of 10% sodium hydroxide solution and then with one portion of water. The ether was removed by evaporation and the residue was crystallized once from alcohol. The yield was 41.5 g. of *p*-tolyl mesitoate, colorless needles melting at 73° (cor.).

*Anal.* Calcd. for C<sub>17</sub>H<sub>18</sub>O<sub>2</sub>: C, 80.30; H, 7.10. Found: C, 80.29; H, 7.10.

*p*-Tolyl 2,4,6-triisopropylbenzoyl chloride and *p*-cresol. It was purified by distillation; b. p. 181–184° (3 mm.); m. p. 66–68° (cor.), from methanol.



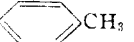
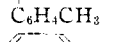

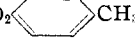

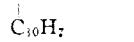

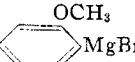
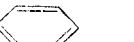
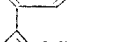

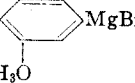



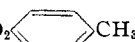
*Anal.* Calcd. for C<sub>23</sub>H<sub>30</sub>O<sub>2</sub>: C, 81.61; H, 8.93. Found: C, 81.67; H, 8.60.

**2,4,6-Triisopropylpropiophenone.**—A solution of 23.1 g. of propionyl chloride in 50 cc. of carbon disulfide was added slowly, with stirring, to a mixture of 55 g. of 1,3,5-triisopropylbenzene, 37.5 g. of anhydrous aluminum chloride and 150 cc. of carbon disulfide at 10°. After addition of the acid chloride was complete, the ice-bath was removed and the reaction mixture was stirred at room temperature for three hours. It was then poured on cracked ice and 200 cc. of concentrated hydrochloric acid. The water layer was extracted with benzene and the extracts were combined with the carbon disulfide solution. This solution was washed with 10% sodium hydroxide solution and water. The solvents were removed and the residue

(3) See Arnold, Bank and Liggett, *THIS JOURNAL*, **68**, 3444 (1941).

(4) Fuson, Corse and McKeever, *ibid.*, **61**, 2010 (1939).

TABLE I  
REACTIONS<sup>a</sup>

Ester	Grignard reagent	Product	Yield, %	Product	Yield, %
MesCO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub> MgBr	MesCO <sub>2</sub> H	50	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br <sup>b</sup>	
MesCO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub> MgI	MesCO <sub>2</sub> H	65	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> I	70
MesCO <sub>2</sub> CH <sub>3</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub> MgBr	MesCO <sub>2</sub> H	25	CH <sub>3</sub> Br	20
MesCO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> MgI	MesCO <sub>2</sub> H	61	<i>n</i> -C <sub>4</sub> H <sub>9</sub> I	54
MesCO <sub>2</sub> CH <sub>3</sub>	MgI	MesCO <sub>2</sub> H	80		
MesCO <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	MgI	MesCO <sub>2</sub> H	97	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	
MesCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	CH <sub>3</sub> MgI	<i>p</i> -Cresol	76	MesCOCH <sub>3</sub>	45 <sup>c</sup>
MesCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> MgBr	<i>p</i> -Cresol	54	MesCOCH <sub>2</sub> CH <sub>3</sub>	61 <sup>d</sup>
MesCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> MgCl	<i>p</i> -Cresol	55	MesCOCOC <sub>6</sub> H <sub>5</sub>	small amount <sup>e</sup>
TipCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	CH <sub>3</sub> MgI	<i>p</i> -Cresol	78	TipCOCH <sub>3</sub>	46 <sup>f</sup>
TipCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub> MgBr	<i>p</i> -Cresol		TipCOCH <sub>2</sub> CH <sub>3</sub>	43 <sup>g</sup>
MesCO <sub>2</sub> 	CH <sub>3</sub>  MgBr	<i>p</i> -Cresol	95	MesCO 	13
				 C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	
					
MesCO <sub>2</sub> 	$\alpha$ -NaphMgBr	<i>p</i> -Cresol	40	MesCO 	trace <sup>h</sup>
				 C <sub>10</sub> H <sub>7</sub>	
MesCO <sub>2</sub> 	 MgBr	<i>p</i> -Cresol	74	MesCO 	13 <sup>i</sup>
					
					
MesCO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	 MgBr	<i>p</i> -Cresol	75	MesCO 	15 <sup>j</sup>
					
					
MesCO <sub>2</sub> 	MesMgBr	<i>p</i> -Cresol	85	MesCOMes	3
				MesCOCOMes	trace

<sup>a</sup> The radicals mesityl and 2,4,6-triisopropylphenyl are represented in the table by Mes and Tip, respectively.

<sup>b</sup> Identified by conversion into benzaldehyde [(Delépine, *Compt. rend.*, 157, 852 (1913)]. <sup>c</sup> Identified by preparation of the 3,5-dinitro derivative; m. p. 140° [Fuson and Walker, *THIS JOURNAL*, 52, 3269 (1930)]. <sup>d</sup> Identified by conversion to  $\alpha,\alpha$ -dibromo-3,5-dinitropropiomesitylene; m. p. 99° [Fisher, Snyder and Fuson, *ibid.*, 54, 3669 (1932)].

<sup>e</sup> Identified by carbon and hydrogen analysis and a mixed melting point determination with an authentic sample. <sup>f</sup> A mixed melting point of this compound with an authentic sample showed no depression. <sup>g</sup> A mixed melting point of this compound with an authentic specimen prepared by the Friedel-Crafts method was not depressed. <sup>h</sup> M. p. 180°, from ethanol-chloroform. *Anal.* Calcd. for C<sub>30</sub>H<sub>24</sub>O: C, 89.95; H, 6.04. Found: C, 89.64; H, 6.35. <sup>i</sup> M. p. 94°, from ethanol. *Anal.* Calcd. for C<sub>23</sub>H<sub>22</sub>O<sub>2</sub>: C, 83.58; H, 6.72. Found: C, 83.53; H, 6.84. <sup>j</sup> M. p. 144°, from alcohol. *Anal.* Calcd. for C<sub>24</sub>H<sub>20</sub>O<sub>3</sub>: C, 79.96; H, 6.72. Found: C, 80.09; H, 6.89.

was distilled under reduced pressure. The yield of 2,4,6-triisopropylpropiophenone, b. p. 123–126° (3 mm.), was 35 g. This ketone melted at 81–83° (cor.) after recrystallization from methanol.

*Anal.* Calcd. for C<sub>18</sub>H<sub>22</sub>O: C, 83.02; H, 10.84. Found: C, 83.10; H, 10.92.

**2,4,6-Triisopropylacetophenone.**<sup>5</sup>—This compound was prepared in a similar manner by condensing acetyl chloride with 2,4,6-triisopropylbenzene. The yield was 53% of the theoretical and the compound melted at 87.5–88° after crystallization from methanol. It is not the same as the compound reported by Koch and Steinbrink.<sup>6</sup>

(5) This experiment was carried out by Dr. E. C. Horning.

(6) Koch and Steinbrink, *Brennstoff-Chem.*, 19, 277 (1938).

*Anal.* Calcd. for C<sub>17</sub>H<sub>20</sub>O: C, 82.85; H, 10.63. Found: C, 82.97; H, 10.59.

**Treatment of Hindered Esters with Grignard Reagents.**—The reactions of several hindered esters with various Grignard reagents have been studied. The results of this work are shown in the table. Since the experimental procedure was very similar for all the reactions carried out, two procedures used will be selected as representative of the methods employed and presented in detail.

***n*-Butyl Mesitoate and Phenylmagnesium Iodide.**—Phenylmagnesium iodide was prepared from 30.6 g. of iodobenzene and 3.6 g. of magnesium in 60 cc. of *n*-butyl ether. Sixty-six grams of *n*-butyl mesitoate dissolved in 35 cc. of *n*-butyl ether was added. The reaction mixture

