

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Reaction of Grignard Reagents with  $\beta$ -Aminonitriles

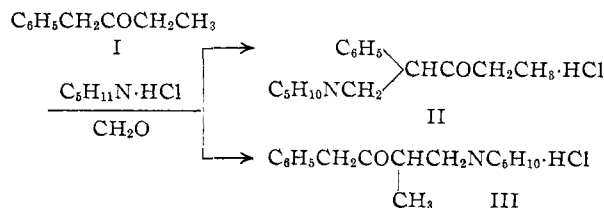
BY A. POHLAND AND H. R. SULLIVAN

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$\beta$ -Dialkylaminoisobutyronitriles have been allowed to react with phenyl- and benzylmagnesium halides to yield the corresponding aminoketones.  $\beta$ -Morpholinopropionitrile and phenylmagnesium bromide yielded  $\beta$ -morpholinopropiophenone. The Mannich reaction with 1-phenyl-2-butanone, formaldehyde and piperidine hydrochloride gave two isomers, 3-methyl-1-phenyl-4-piperidino-2-butanone and 2-phenyl-1-piperidino-3-pentanone.

A number of benzyl  $\beta$ -dialkylaminoethyl ketones were needed as intermediates for the synthesis of compounds to be tested for analgesic activity. Phenylacetone, under the Mannich conditions, undergoes reaction at the methylene carbon to yield 4-dialkylamino-3-phenyl-2-butanones.<sup>1</sup> 1,1-Diphenylacetone is reported to react only at methyl carbon to yield benzhydryl  $\beta$ -dialkylaminoethyl ketones.<sup>2</sup>

The reaction of 1-phenyl-2-butanone (I) with piperidine and formaldehyde was investigated. The possibility that both methylene groups might react under the Mannich conditions was anticipated. Two products, 2-phenyl-1-piperidino-3-pentanone (II) and 3-methyl-1-phenyl-4-piperidino-2-butanone (III), were isolated.



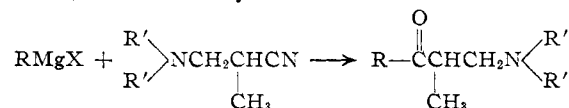
Compound II was deaminated to 2-phenyl-3-pentanone by the method of Schultz<sup>1</sup> using hydrogen over Raney nickel.

It has been reported that Grignard reagents do not react with  $\beta$ -dialkylaminopropionitriles to form ketones.<sup>3,4</sup> We have attempted several reactions of  $\beta$ -piperidinopropionitrile with phenylmagnesium bromide and also phenyllithium and were unable to isolate  $\beta$ -piperidinopropiophenone, thus confirming previous reports. Benzylmagnesium bromide, however, did add to  $\beta$ -piperidinopropionitrile to a slight extent. The 1-phenyl-4-piperidino-2-butanone was not isolated as such but was reduced in crude form using lithium aluminum hydride to the carbinol.

In one case it was possible to obtain a good yield of an aminoketone from a  $\beta$ -aminopropionitrile. It was suspected that the less basic  $\beta$ -morpholinopropionitrile might be less liable to eliminate the amine during the Grignard reaction. The reaction of  $\beta$ -morpholinopropionitrile with phenylmagnesium bromide yielded 49% of  $\beta$ -morpholinopropiophenone.

While  $\beta$ -dialkylaminopropionitriles were not useful for the preparation of the aminoketones, it was found that the  $\beta$ -dialkylaminoisobutyronitriles

could be converted to aminoketones in good yields. Three  $\beta$ -aminoisobutyronitriles



were prepared by the reaction of methacrylonitrile with dimethylamine, piperidine and pyrrolidine. Phenylmagnesium bromide and also phenyllithium reacts with  $\beta$ -piperidinoisobutyronitrile to yield 32 and 64%, respectively, of the  $\beta$ -piperidinoisobutyrophenone. Benzylmagnesium chloride and  $\beta$ -piperidinoisobutyronitrile yields 51% of 3-methyl-1-phenyl-4-piperidino-2-butanone (III) which had previously been obtained from the Mannich reaction using 1-phenyl-2-butanone. Table I summarizes the data on ketones prepared in this manner.

**Acknowledgment.**—The authors are indebted to W. L. Brown, G. L. Maciak, H. L. Hunter and Miss Gloria Beckmann for the microanalyses.

Experimental<sup>5</sup>

**Reaction of 1-Phenyl-2-butanone with Piperidine and Formaldehyde.**—A reaction mixture containing 14.8 g. (0.1 mole) of 1-phenyl-2-butanone, 12.2 g. (0.1 mole) of piperidine hydrochloride, 4.5 g. (0.15 mole) of paraformaldehyde, 0.25 ml. of concentrated hydrochloric acid and 30 ml. of absolute ethanol was refluxed for one hour. An additional 3.0 g. (0.1 mole) of paraformaldehyde was added and the reflux continued for three hours. The ethanol was removed *in vacuo* and the residue dissolved in water. The aqueous solution was washed with ether and made alkaline with concentrated ammonium hydroxide. The insoluble oil was taken up in ether and dried over magnesium sulfate. The hydrochloride was prepared using the ether solution and anhydrous hydrogen chloride. Fractional crystallization from methanol-ethyl acetate yielded two isomers. The less soluble isomer, 3-methyl-1-phenyl-4-piperidino-2-butanone hydrochloride (III), crystallized in heavy prisms which melted at 162–163°, weight 7.0 g. (28%).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{23}\text{NO}\cdot\text{HCl}$ : C, 68.19; H, 8.58; N, 4.97. Found: C, 68.30; H, 8.71; N, 4.91.

The more soluble isomer, 2-phenyl-1-piperidino-3-pentanone hydrochloride (II), crystallized in light fluffy plates which melted at 169°, weight 7.0 g. (28%).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{23}\text{NO}\cdot\text{HCl}$ : C, 68.19; H, 8.58; N, 4.97. Found: C, 68.40; H, 8.86; N, 4.75.

**Deamination of 2-Phenyl-1-piperidino-3-pentanone (II).**—Following the procedure of Schultz,<sup>1</sup> 5 g. of the aminoketone hydrochloride in 100 ml. of ethanol was hydrogenated for 3 hours at 80° and 1200 p.s.i. of hydrogen using Raney nickel catalyst. The ketone was not isolated but converted to the semicarbazone and recrystallized from ethanol-water in platelets which melted at 135–136°. 2-Phenyl-3-pentanone semicarbazide is reported in the literature to melt at 135–136°.<sup>1</sup>

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{17}\text{N}_3\text{O}$ : C, 65.72; H, 7.81; N, 19.16. Found: C, 65.49; H, 8.01; N, 19.08.

**1-Phenyl-4-piperidino-2-butanone.**—Benzylmagnesium bromide was prepared from 136 g. (0.8 mole) of benzyl

(5) Melting points and boiling points are uncorrected.

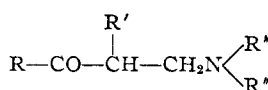
(1) E. M. Schultz and J. B. Bicking, *THIS JOURNAL*, **75**, 1128 (1953).

(2) L. Katz and L. S. Karger, *ibid.*, **74**, 4085 (1952).

(3) P. Bruylants, *Bull. soc. chim. Belg.*, **32**, 266 (1923).

(4) D. E. Clark and H. S. Mosher, *THIS JOURNAL*, **73**, 1026 (1950).

TABLE I



R	R'	(R'') <sub>2</sub> N-	M.p., °C. HCl	Yield, %	Mol. formula	Carbon		Hydrogen, %		Nitrogen	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	CH <sub>3</sub>	C <sub>8</sub> H <sub>10</sub> N <sup>-a</sup>	162-163	45	C <sub>16</sub> H <sub>22</sub> NO·HCl	68.19	68.27	8.58	8.53	4.97	4.79
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	CH <sub>3</sub>	C <sub>4</sub> H <sub>8</sub> N <sup>-b</sup>	121-122	30	C <sub>15</sub> H <sub>21</sub> NO·HCl	67.27	67.56	8.28	8.60	5.23	5.20
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	CH <sub>3</sub>	(CH <sub>3</sub> ) <sub>2</sub> N-	126-127	45	C <sub>15</sub> H <sub>19</sub> NO·HCl	64.58	64.35	8.34	8.35	5.80	5.90
C <sub>6</sub> H <sub>5</sub>	H	C <sub>4</sub> H <sub>8</sub> ON <sup>-c</sup>	178-179 <sup>d</sup>	49	C <sub>15</sub> H <sub>17</sub> NO <sub>2</sub> ·HCl						
C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	C <sub>8</sub> H <sub>10</sub> N-	176 <sup>e</sup>	32	C <sub>15</sub> H <sub>21</sub> NO·HCl						

<sup>a</sup> Piperidino. <sup>b</sup> Pyrrolidino. <sup>c</sup> Morpholino. <sup>d</sup> R. H. Haradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1939), reports m.p. 177°. <sup>e</sup> Reference (6) reports m.p. 176.2-177°.

bromide and 30.5 g. (1.25 moles) of magnesium in 750 ml. of ether. The Grignard solution was decanted from the excess magnesium and 69 g. (0.5 mole) of 3-piperidinopropionitrile was added dropwise with stirring. The reaction was decomposed by pouring onto ice and dilute hydrochloric acid. The aqueous layer was made basic with ammonium hydroxide and extracted with 200 ml. of ether. The ether extract was dried over magnesium sulfate.

The dried ether extract was added dropwise with stirring to 10 g. of lithium aluminum hydride in 200 ml. of ether. The reaction was decomposed with water and the ether solution dried over magnesium sulfate. The ether was distilled and the residual oil distilled *in vacuo*. The fraction boiling at 148-152° (0.8 mm.), weight 4.5 g., was collected. The hydrochloride was prepared in ether using anhydrous hydrogen chloride. The 1-phenyl-4-piperidinobutanone hydrochloride was recrystallized three times from methanol-ethyl acetate, m.p. 124-125°; weight 2.2 g. (1.6%).

*Anal.* Calcd. for C<sub>15</sub>H<sub>23</sub>NO·HCl: C, 66.77; H, 8.97; N, 5.19; Cl, 13.14. Found: C, 66.80; H, 8.98; N, 4.94; Cl, 13.14.

**β-Pyrrolidinoisobutyronitrile.**—A reaction mixture containing 156.5 g. (2.2 moles) of pyrrolidine, 148 g. (2.2 moles) of methacrylonitrile and 4 ml. of 40% benzyltrimethylammonium hydroxide was refluxed for five hours. An additional 4 ml. of benzyltrimethylammonium hydroxide was added and the reaction mixture refluxed overnight. The product boiled at 62° (0.8 mm.); *n*<sub>D</sub><sup>25</sup> 1.4558; weight 238.4 g. (76%).

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.36; H, 10.26; N, 20.60.

**β-Piperidinoisobutyronitrile.**—Prepared by the procedure above for the pyrrolidine compound using 148 g. (2.2 moles) of methacrylonitrile, 170.2 g. (2.0 moles) of piperidine and 16 ml. of benzyltrimethylammonium hydroxide. The product distilled at 60-61° (0.2 mm.); *n*<sub>D</sub><sup>25</sup> 1.4598; weight 245.4 g. (80%).

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>: C, 71.00; H, 10.60; N, 18.40. Found: C, 71.09; H, 10.44; N, 17.74.

The hydrochloride was prepared in anhydrous ether and recrystallized from methanol-ethyl acetate, m.p. 181-182°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>·HCl: C, 57.28; H, 9.08; N, 14.85. Found: C, 57.27; H, 9.02; N, 14.68.

**β-Dimethylaminoisobutyronitrile.**—A solution of 170 g. (3.8 moles) of dimethylamine and 5 ml. of 40% benzyltrimethylammonium hydroxide was cooled to 5° during the dropwise addition of 136 g. (2.0 moles) of methacrylonitrile. The reaction was allowed to stand at room temperature overnight and was then washed with 400 ml. of dilute hydrochloric acid. The aqueous extract was made alkaline with 50% sodium hydroxide and the oil dried in ether solution

over magnesium sulfate. The product boiled at 55-56° (6.0 mm.); *n*<sub>D</sub><sup>25</sup> 1.4210; weight 180 g. (80%).

The hydrochloride was prepared in ether using anhydrous hydrogen chloride and after three recrystallizations from methanol-ethyl acetate melted at 171-172°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>·HCl: C, 48.48; H, 8.81; N, 18.85. Found: C, 48.18; H, 8.97; N, 18.87.

### 3-Methyl-1-phenyl-4-piperidino-2-butanone. (III).—

Benzylmagnesium chloride was prepared from 38.0 g. (1.56 moles) of magnesium, 76.0 g. (0.60 mole) of benzyl chloride and 600 ml. of ether. The Grignard solution was stirred at room temperature during the dropwise addition of 45.6 g. (0.30 mole) of β-piperidinoisobutyronitrile. The reaction mixture was stirred and refluxed for two hours and then decomposed with 200 ml. of saturated ammonium chloride solution. The ether solution was decanted from the granular solid and dried over anhydrous magnesium sulfate. The hydrochloride salt of the product was prepared using anhydrous hydrogen chloride and after three recrystallizations from methanol-ethyl acetate melted at 162-163°, weight 38.0 g. (45%).

**Phenylmagnesium Bromide and β-Piperidinoisobutyronitrile.**—Phenylmagnesium bromide was prepared from 66.0 g. (0.42 mole) of bromobenzene, 10.3 g. (0.42 mole) of magnesium and 500 ml. of anhydrous ether. The Grignard solution was cooled during the dropwise addition of 30.0 g. (0.20 mole) of β-piperidinoisobutyronitrile in 100 ml. of anhydrous ether. The reaction mixture was refluxed for two hours and then decomposed by pouring into ice and dilute hydrochloric acid. The aqueous layer was washed with ether and made alkaline with concentrated ammonium hydroxide. The oil was dried in ether over magnesium sulfate. The product boiled at 122° (0.5 mm.), weight 14.9 g. (32%). The hydrochloride was prepared and recrystallized from methanol-ethyl acetate, m.p. and mixed m.p. 176° with an authentic sample.<sup>8</sup>

**Phenyllithium and β-Piperidinoisobutyronitrile.**—Phenyllithium was prepared from 50.5 g. (0.32 mole) of bromobenzene, 4.4 g. (0.64 g. atom) of lithium ribbon and 200 ml. of anhydrous ether. The phenyllithium solution was stirred at room temperature during the dropwise addition of 30.0 g. (0.20 mole) of β-piperidinoisobutyronitrile in 100 ml. of anhydrous ether. The reaction mixture was stirred for one hour at room temperature and then decomposed by pouring into ice and hydrochloric acid. The acid aqueous solution was washed with ether and then made alkaline with concentrated ammonium hydroxide. The liberated oil was taken up in ether and dried over anhydrous magnesium sulfate. The product boiled at 122-123° (0.30 mm.); *n*<sub>D</sub><sup>25</sup> 1.5292; weight 29.8 g. (64%).

### INDIANAPOLIS, INDIANA

(6) A. W. Ruddy and J. S. Buckley, Jr., *THIS JOURNAL*, **72**, 718 (1950).