

containing 25 ml. of N-ethylmorpholine (total volume was 250 ml.) and 5 g. of a palladium charcoal catalyst containing 5% palladium were treated as above under an initial hydrogen pressure of 2500 pounds. Reduction was carried out at 175°, and the absorption of one mole of hydrogen required between ten and fifteen hours. After removing the catalyst by filtration, ether was added to the solution which was then extracted with dilute hydrochloric acid to remove the N-ethylmorpholine. If this were not done, the solution turned dark because of the effect of the base on  $\beta$ -tetralone. The clear, orange-yellow solution was washed with water, dried over anhydrous sodium sulfate and distilled under reduced pressure. Fifty grams of a fraction b. p. 116–135° at 5 mm. was obtained, and on shaking with

a saturated sodium bisulfite solution gave 50 g. (40%) of the bisulfite addition compound of  $\beta$ -tetralone. The  $\beta$ -tetralone recovered from several experiments was identified as its semicarbazone m. p. 193–194° (reported m. p. 193°).<sup>8</sup>

### Summary

The preparation of  $\beta$ -tetralone by the high pressure catalytic hydrogenation of  $\beta$ -naphthol with a palladium catalyst is described.

The mechanism of this reaction is briefly considered.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND CO.]

## Analgesics. I. N-Alkylated-1,2-diphenylethylamines Prepared by the Leuckart Reaction

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The preparation of amines from aldehydes and ketones by their reaction with excess ammonium formate has come to be known as the Leuckart reaction. In a recent paper by F. S. Crossley and M. L. Moore<sup>3</sup> the bibliography for the work on this reaction is given along with some of their own results and views on the reaction mechanism.

In the present investigation the Leuckart reaction has been utilized in the preparation of N-alkylated-1,2-diphenylethylamines. Two other amines not belonging to this series are included for purposes of comparison. The primary amines and formic acid were mixed and used in the reaction with ketones without isolating the intermediate ammonium salts or formamides. As may be seen from the summary of the results (Table I), the yields of N-alkylated-1,2-diphenylethylamine varied from 5 to 36%. At first glance it would appear that these low yields are due to the activating influence of the phenyl groups and the ease with which the resulting amines cleave to give stilbene derivatives and aliphatic amines. That this explanation is not sufficient is shown by the reaction of formamide on desoxyanisoin where a yield of 75% of 1,2-di-*p*-methoxyphenylethylamine was obtained (Table I). Neither should the low yields be attributed solely to the presence of the alkyl group on the formamide since Novelli,<sup>4</sup> in his experiments on the Leuckart reaction, employed the formamides prepared from methyl, ethyl and butyl amines on *p*-chloroacetophenone and obtained yields of 70–80% of the corresponding secondary amines.

When sufficient quantities of the amines for pharmacological testing had been obtained, there was usually no attempt to work out the optimum conditions. However, the time, temperature and

catalyst were varied somewhat in an attempt to improve the yield of N-methyl-1,2-di-*p*-methoxyphenylethylamine. In each of these cases approximately four moles of methyl formamide was treated with one mole of desoxyanisoin. It appeared that the addition of a few grams of acetic acid or sodium acetate had little or no effect in promoting the reaction whether it be added at the beginning or in small portions throughout the reaction. Temperatures of 140° or below gave no appreciable reaction and the starting materials were recovered unchanged. In another experiment the mixture was heated to 225° for six hours; this gave none of the desired product and the starting ketone could not be recovered. In this particular experiment the neutral fraction was crystallized from acetic acid to give a little di-*p*-methoxystilbene, m.p. 210–211°, which gave no depression of its melting point on mixing with an authentic sample. This derivative was presumably formed by the pyrolysis of the formyl derivative of the N-methyl-1,2-di-*p*-methoxyphenylethylamine. Of the conditions tried, those listed in the table for this compound appear to be the best.

It is particularly interesting to note that  $\beta$ -diethylaminoethylamine and ethanolamine may be used in the Leuckart reaction to give secondary amines possessing the  $\beta$ -diethylaminoethyl- or  $\beta$ -hydroxyethyl groups, respectively.

The salts of these compounds, if soluble to the extent of 1% or more in water, were tested for their analgesic action on mice by Professor Harald Holck of the School of Pharmacy, University of Nebraska. Whereas detailed pharmacology on these compounds will be published at a later date, preliminary results indicate that N-methyl-1,2-di-*p*-methoxyphenylethylamine and N-methyl-1-*p*-methoxyphenyl-2-phenylethylamine do possess some analgesic activity but are less active than isonipecaine.

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(4) A. Novelli, *This Journal*, **61**, 520 (1939).

TABLE I  
 SUMMARY OF REACTIONS

Amine	B. p. of base, °C.	Mm.	M. p. hydrochloride, °C.	Temp. of reaction	Reaction time, hrs.	Catalyst	Yield based on ketone, %	Empirical formula	Analyses, % Calcd.	Found
N-Methyl-1,2-diphenylethyl <sup>a</sup>	160-161	8	184-186 <sup>b</sup>	180-190	3	.....	8	C <sub>18</sub> H <sub>19</sub> ClN	Cl, 14.35	Cl, 14.44
N-Ethyl-1,2-diphenylethyl <sup>a</sup>	162-164	3	236-238 <sup>c</sup>	165-185	8	O	34	C <sub>18</sub> H <sub>21</sub> ClN	N, 5.35	N, 5.45
N-Propyl-1,2-diphenylethyl <sup>a</sup>	.....	..	214-216 <sup>c</sup>	160-190	4	NaOAc	15	C <sub>17</sub> H <sub>21</sub> ClN	276	280 <sup>d</sup>
N- <i>i</i> -Propyl-1,2-diphenylethyl <sup>a</sup>	.....	..	256-257	185-210	2	O	20	C <sub>17</sub> H <sub>21</sub> ClN	N, 5.08	N, 4.90
N- <i>i</i> -Butyl-1,2-diphenylethyl <sup>a</sup>	.....	..	249-251	165-185	5	NaOAc	11	C <sub>19</sub> H <sub>23</sub> ClN	N, 4.82	N, 4.62
N- $\beta$ -Hydroxy-ethyl-1,2-diphenylethyl	208	9	202-204 <sup>e</sup>	160-180	3	O	31	C <sub>16</sub> H <sub>19</sub> ClNO	277.8	279 <sup>d</sup>
N-( $\beta$ -N-Morpholinoethyl)-1,2-diphenylethyl	.....	..	142 <sup>f</sup>	160-205	3	AcOH	13	C <sub>20</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>2</sub> O	Cl, 18.49	Cl, 18.48
N- $\beta$ -Diethylaminoethyl-1,2-diphenylethyl	170-185	4	.....	180-190	3	AcOH	36	C <sub>20</sub> H <sub>25</sub> N <sub>2</sub> <sup>h</sup>	N, 9.45	N, 9.43
N-Methyl-1- <i>p</i> -methoxyphenyl-2-phenylethyl <sup>g</sup>	116-126	0.1	139-141 <sup>f</sup>	205-230	3.5	AcOH	10.5	C <sub>18</sub> H <sub>20</sub> ClNO	Cl, 12.76	Cl, 12.61
N-Methyl-1,2-di- <i>p</i> -methoxyphenylethyl	232-236	20	157-159 <sup>b</sup> 60-61 <sup>i</sup>	160-180	14	AcOH	15	C <sub>17</sub> H <sub>21</sub> ClNO <sub>2</sub>	Cl, 11.51	Cl, 11.49
N-Ethyl-1,2-di- <i>p</i> -methoxyphenylethyl <sup>a</sup>	206-207	4	167-169 <sup>j</sup> 65-70 <sup>k</sup>	139-163	11	O	12	C <sub>18</sub> H <sub>21</sub> NO <sub>2</sub>	N, 4.91	N, 4.96
N-Butyl-1,2-di- <i>p</i> -methoxyphenylethyl	.....	..	192-195 <sup>c</sup>	180-145	3	AcOH	5	C <sub>20</sub> H <sub>25</sub> ClNO <sub>2</sub>	350	350 <sup>d</sup>
1,2-Di- <i>p</i> -methoxyphenylethyl- <sup>a,k</sup>	.....	..	214-217 <sup>c</sup>	160-180	5	AcOH	75	C <sub>16</sub> H <sub>20</sub> ClNO <sub>2</sub>	294	296 <sup>d</sup>
N-Methylbenzohydryl <sup>l</sup>	158	4	.....	180-214	7	O	31	C <sub>14</sub> H <sub>15</sub> N	211	214 <sup>d</sup>

\* These compounds have been tested for their pressor action, broncho-dilator effects, and central nervous system stimulation; Tainter, Luduena, Lackey and Neuru, *J. Pharmacol.*, **77**, 317-323 (1943). <sup>b</sup> Crystallized from acetone plus 1% water. <sup>c</sup> Crystallized from water. <sup>d</sup> Neutral equivalent. <sup>e</sup> Crystallized from dilute hydrochloric acid. <sup>f</sup> Crystallized from alcohol-ether mixtures. <sup>g</sup> Prepared by R. F. Shrimpton of this Laboratory. <sup>h</sup> Analysis by Marie Gilliland of this Laboratory. <sup>i</sup> M. p. of free base. <sup>j</sup> Precipitated from ether with hydrochloric acid. <sup>k</sup> Dodds, Lawson and Williams, *Proc. Roy. Soc. (London)* **B132**, 119 (1944). <sup>l</sup> Semper and Lichtenstadt, *Ber.*, **51**, 934 (1918).

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### Experimental

The ketones used in this reaction were desoxybenzoin, desoxyanisoin, *p*-methoxyphenyl benzyl ketone<sup>b</sup> and benzophenone. The primary amines used were methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl,  $\beta$ -hydroxyethyl,  $\beta$ -diethylaminoethyl,  $\beta$ -*N*-morpholinoethyl amines. The starting materials which were not available commercially were prepared by standard methods. The formic acid used was the 90% technical grade. The reaction was carried out in a distillation apparatus so that the water or the alkyl formamide could be distilled out to raise the reaction temperature to the desired point. The conditions of time, temperature and catalyst were varied as noted in Table I. A specific example is given by way of illustration.

**N-*n*-Propyl-1,2-diphenylethylamine.**—To 200 g. of 45% formic acid was added slowly with cooling 120 g. of *n*-propylamine. Next 100 g. of desoxybenzoin was added

and the water was distilled from the mixture. When the water was gone, 10 g. of fused sodium acetate was added and the mixture was heated for four hours during which time the temperature rose slowly from 160 to 190°. The mixture was now cooled and washed with 300 cc. of water to remove the excess *N*-propyl formamide. The oily material was now boiled one hour with 500 cc. of 10% hydrochloric acid and then boiled with two successive 500-cc. portions of water to make certain that extraction of the hydrochloride of the product was complete. The extracts were combined and cooled to give crystals of *N-n*-propyl-1,2-diphenylethylamine hydrochloride. After recrystallization from water this melted at 214-216° (15% yield). Neutral equivalent calculated for C<sub>17</sub>H<sub>21</sub>ClN: 276. Found: 280.

### Summary

1. Twelve new substituted 1,2-diphenylethylamines have been prepared by the Leuckart reaction.

2. Two of these compounds possess some analgesic action.

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(5) Buck and Ide, *This Journal*, **53**, 1536 (1931).