

The filtrate and washings were extracted with 700 cc. of 5% sodium hydroxide solution in 100-cc. portions and then with 300 cc. of water in 100-cc. portions. No phenol was present in the alkaline washings. The ether solution, dried over magnesium sulfate was concentrated to a residue which was distilled giving 3.0 g. of benzyl alcohol-O<sup>18</sup>, b.p. 49° at 1 mm. Evaporative distillation at 5 mm. gave material  $n_D^{20}$  1.5372, containing  $1.13 \pm 0.02$  atom % excess oxygen-18 (Table I: J).

*Anal.* Calcd. for C<sub>7</sub>H<sub>8</sub>O: C, 77.8; H, 7.5. Found: C, 77.5; H, 7.2.

The precipitate obtained above was dissolved in 10% aqueous sulfuric acid and extracted with 450 cc. of ether. The ether extract was washed with 50 cc. of water and ex-

tracted with 100 cc. of 5% sodium hydroxide. This solution was washed with ether, acidified and extracted with 160 cc. of ether in four portions. The ether extract was washed successively with 40 cc. of water and with 40 cc. of saturated sodium bicarbonate solution and then was concentrated. The residue was distilled at 1 mm. collecting all volatile material in a Dry Ice trap. Redistillation under nitrogen gave 2.0 g. of phenol; b.p. 175–180° at 770 mm.; m.p. 38–39°. The phenol contained  $0.001 \pm 0.005$  atom % excess of oxygen-18 (Table I: P).

*Anal.* Calcd. for C<sub>6</sub>H<sub>6</sub>O: C, 76.6; H, 6.2. Found: C, 76.8; H, 6.4.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

### Catalytic Debenzylation. III. The Influence of $\alpha$ -Substitution on the Ease of Hydrogenolysis<sup>1</sup>

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The effect on the ease of hydrogenolysis of  $\alpha$ -substitution in benzyl groups has been investigated. A methyl group in the  $\alpha$ -position lessens the ease of cleavage to about the same extent as one in the ring. Benzyl and phenyl groups have a smaller influence. The block against hydrogenolysis exerted by certain groups ( $-\text{COOR}$  and  $-\text{CH}_2\text{NR}_3^+$ ) attached to the benzylic carbon atom is removed by interpolation of one methylene radical.

Earlier papers in this series<sup>2,3</sup> have dealt mainly with the effect of substitution in the aromatic nucleus on the stability of benzyl groups toward hydrogenolysis. The present paper extends the observations made in Part I<sup>2</sup> on the effect of  $\alpha$ -substitution in the benzyl radical. There it was shown that the groups  $-\text{COOH}$ ,  $-\text{CONH}_2$ ,  $-\text{COOR}$  or  $-\text{CH}_2\text{NR}_3^+$  in the  $\alpha$ -position prevented debenzylation under our standard conditions. Using more stringent conditions the debenzylation of mandelic acids and phenylethanolamines has been achieved.<sup>4,5</sup>

The hydrogenolysis of a number of derivatives homologous with the first series was carried out with a view to finding out how far these groups could be removed without losing their effect. Ethyl benzoylacetate in methanol containing a palladized charcoal catalyst absorbed two mols of hydrogen. The reaction slowed after the absorption of slightly more than one mol of hydrogen (reduction of the ketone to an alcohol) and the final mol of hydrogen (debenzylation) was absorbed at about one-tenth the rate of the reduction of benzyl alcohol. Ethyl nicotinoylacetate on reduction also lost the  $\beta$ -oxygen but at a rather slow rate. It should be noted that in this instance the substituted benzyl residue of the (unisolated) ethyl  $\beta$ -phenyl- $\beta$ -hydroxypropionate is replaced by a substituted 3-pyridylmethyl group.  $\beta$ -Dimethylaminopropiophenone hydrochloride<sup>6</sup> was reduced smoothly to  $\gamma$ -phenylpropyldimethylamine hydrochloride. It

is thus apparent that the interpolation of one methylene group between the benzylic hydroxyl and the interfering  $\alpha$ -group in both mandelic acid and phenylethanolamine compounds permits debenzylation to proceed although with somewhat diminished ease.

The previous papers in this series<sup>2,3</sup> have utilized the competitive debenzylation of dibenzylmethylamines, usually as the hydrochlorides, with a different substituent in each of the benzyl radicals to demonstrate the effects of these substituents. The same method was turned to a study of the effects of  $\alpha$ -substitution. In the series of experiments, the results of which are reported in Table I, the tertiary amine hydrochlorides in dilute solution in methanol (0.01–0.02 mole in 50 ml. of methanol) were shaken with hydrogen at about 2 atm. over-pressure in the presence of palladized charcoal. The mixture of products was analyzed usually by crystallization of the hydrochlorides of the secondary bases.

The almost unilateral cleavage of  $\alpha$ -phenethylbenzylmethylamine hydrochloride to  $\alpha$ -phenethylmethylamine hydrochloride (reduction 1, Table I) indicates that the presence of a methyl substituent in the  $\alpha$ -position stabilizes the C–N bond. The reduction of  $\alpha$ -phenethyl-*p*-methylbenzylmethylamine hydrochloride to an inseparable mixture of  $\alpha$ -phenethylmethylamine and *p*-methylbenzylmethylamine hydrochlorides (reduction 2) indicates that the effect of a methyl group in the  $\alpha$ -position is very similar to the effect of the same group in the *p*-position. This is confirmed by the observations that the stabilizing effect of an  $\alpha$ -methyl group is less than that of a *p*-methoxyl (reduction 3) and greater than that of a *p*-amino group (reduction 4). In the previous papers of this series<sup>2,3</sup> it was demonstrated that the order of *p*-substituents in stabilizing the C–N bond is: Class I ( $-\text{OMe}$ ,  $-\text{OH}$ ,  $-\text{NH}$

(1) Presented in part before the Division of Organic Chemistry at the 122nd Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1952.

(2) R. Baltzly and J. S. Buck, *THIS JOURNAL*, **65**, 1984 (1943).

(3) R. Baltzly and P. B. Russell, *ibid.*, **72**, 3410 (1950).

(4) K. Kindler, *et al.*, *Ann.*, **554**, 9 (1943); *Ber.*, **74**, 315 (1941); **76**, 1211 (1943); **77**, 585 (1944).

(5) K. W. Rosenmund and E. Karg, *ibid.*, **75**, 1850 (1942).

(6) We wish to thank Dr. D. W. Adamson (Wellcome Research Laboratories, Chemical Division, Beckenham, Kent, England) for this substance.

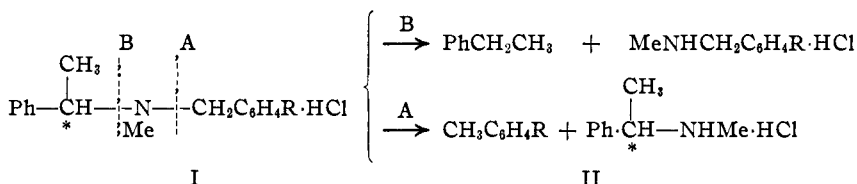
TABLE I  
 COMPETITIVE DEBENZYLATIONS

Reduction no.	Substrate (dotted lines indicate cleavage)	Products (isolated or demonstrated)
1	$\text{C}_6\text{H}_5\text{CH}_2\text{NMeCHMeC}_6\text{H}_5 \cdot \text{HCl}$	$\text{C}_6\text{H}_5\text{CHMe} \cdot \text{NHMe} \cdot \text{HCl}$ (>90%)
2	$p\text{-dl-CH}_3\text{C}_6\text{H}_4\text{-CH}_2\text{NMeCHMeC}_6\text{H}_5 \cdot \text{HCl}$	Inseparable mixture of products
2a	$p\text{-d-CH}_3\text{C}_6\text{H}_4\text{-CH}_2\text{NMeCHMeC}_6\text{H}_5 \cdot \text{HCl}$	40 to 45% $d\text{-C}_6\text{H}_5\text{CHMe} \cdot \text{NHMe} \cdot \text{HCl}$
3	$p\text{-MeOC}_6\text{H}_4\text{-CH}_2\text{NMeCHMeC}_6\text{H}_5 \cdot \text{HCl}$	$p\text{-MeOC}_6\text{H}_4\text{-CH}_2\text{NHMe} \cdot \text{HCl}$ (>80%)
4	$p\text{-NH}_2\text{C}_6\text{H}_4\text{-CH}_2\text{NMeCHMeC}_6\text{H}_5 \cdot \text{HCl}^a$	$p\text{-CH}_3\text{CONHC}_6\text{H}_4\text{-CH}_3$ (90-95%) $\text{C}_6\text{H}_5\text{CHMe} \cdot \text{NHMe} \cdot \text{HCl}$ (>75%)
5	$\text{C}_6\text{H}_5\text{CH}_2\text{NMeCH(C}_6\text{H}_5)_2 \cdot \text{HCl}$	$(\text{C}_6\text{H}_5)_2\text{CHNHMe} \cdot \text{HCl}^b$ (70%) $\text{C}_6\text{H}_5\text{CH}_2\text{NHMe} \cdot \text{HCl}$ (20-25%) $\text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5$ (20-30%)
5a	$\text{C}_6\text{H}_5\text{CH}_2\text{NMeCH(C}_6\text{H}_5)_2$ (base)	$(\text{C}_6\text{H}_5)_2\text{CHNHMe} \cdot \text{HCl}^b$ (10-15%) $\text{C}_6\text{H}_5\text{CH}_2\text{NHMe} \cdot \text{HCl}$ (ca. 80%) $\text{C}_6\text{H}_5\text{CH}_2\text{C}_6\text{H}_5$ (60-70%)
6	$\text{C}_6\text{H}_5\text{CH}_2\text{NMe-CH(C}_6\text{H}_5)_2 \cdot \text{HCl}$	$\text{C}_6\text{H}_5\text{CH}_2\text{CH(C}_6\text{H}_5)_2\text{NHMe} \cdot \text{HCl}^c$ (60%) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$ (10-15%)

<sup>a</sup> The corresponding nitro compound was actually employed. <sup>b</sup> M. Busch and L. Leefhelm, *J. prakt. Chem.*, [2] 77, 20 (1908). <sup>c</sup> L. H. Goodson, C. J. W. Wiegand and P. S. Splitter, *THIS JOURNAL*, 68, 2174 (1946).

$\text{OCH}_3$ ,  $-\text{COOCH}_3$  and  $\text{Cl}$ ) > Class II (Me and  $\text{NH}_3^+$ ) > Class III ( $-\text{NH}_2$ ).

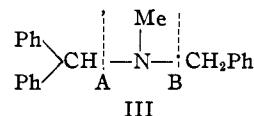
A more precise method for analyzing the products of hydrogenolysis of an  $\alpha$ -phenethyl tertiary amine is presented through the use of optically active materials. Cleavage along the line B in formula I results in loss of optical activity whereas cleavage



A retains the asymmetric carbon atom in II. Thus, if the specific rotation of pure II is known, the amount of II in the cleavage product is readily determined. This method has been applied to the products of reduction 2 and indicates that the  $p$ -methylbenzyl group is removed to the extent of 40 to 45%.

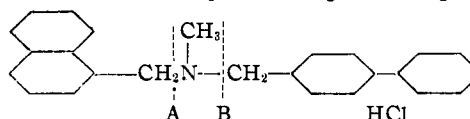
The  $\alpha$ -benzyl group (reduction 6) also has some stabilizing influence on the adjacent C-N link, but the effect of an  $\alpha$ -phenyl group is rather anomalous. Some time after we had observed the cleavage shown in reduction 5, a series of papers by Dahn, Solms and Zoller<sup>7-9</sup> on the hydrogenolysis of benzylic groups was published. These authors stated<sup>9</sup> that the hydrogenolysis of benzhydrylbenzylmethylamine base gave a 75% yield of diphenylmethane and an 85% yield of benzylmethylamine. This represents an almost unilateral cleavage along the line A in formula III whereas we had observed a preponderant cleavage along line B with the hydrochloride. Repetition of these

hydrogenolyses both in these laboratories and by Professor Dahn<sup>10</sup> in Basel has shown that both observations were in fact correct. The reversal in the direction of cleavage in III as between the base and the salt does not appear to be a general phenomenon. Several other dibenzylmethylamines that had previously been debenzylated as the hydrochlorides<sup>3</sup> were reduced as the free bases with results similar to those previously recorded. The only obvious explanation of this unexpected reversal in the direction of cleavage is that there is sufficient steric difference between the tertiary base and its cation to alter its adsorption on the catalyst.<sup>11</sup>



(10) Private communication from Professor Dahn, University of Basel.

(11) The other findings of the Basel group<sup>7-9</sup> are in excellent accord with the past results reported from this Laboratory.<sup>2,3</sup> Dahn, *et al.*, have reported virtually unilateral cleavage of the menaphthylmethyl- $p$ -phenylbenzylamines with removal of the menaphthyl residues (cleavage A below). Earlier reports from these laboratories<sup>2</sup> stated that  $\alpha$ -menaphthylmethyl- $p$ -phenylbenzylamine hydrochloride was cleaved bilaterally. Actually only  $p$ -phenylbenzylmethylamine hydrochloride was isolated, indicating cleavage along line A, and since this product was not quite homogeneous it was then believed to be contaminated with the alternative product arising from cleavage on line B.



In view of this it is not considered that the results of Dahn are in serious conflict with those reported from these laboratories.

(7) H. Dahn and U. Solms, *Helv. Chim. Acta*, **35**, 1162 (1952).

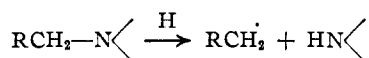
(8) H. Dahn and P. Zoller, *ibid.*, **35**, 1348 (1952).

(9) H. Dahn, U. Solms and P. Zoller, *ibid.*, **35**, 2117 (1952).

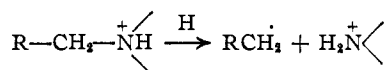
The present status of our knowledge of hydrogenolysis is not favorable to theoretical interpretation. As far as the present work is concerned all that can be said is that a group in the  $\alpha$ -position stabilizes the adjacent C-N bond in the order:  $-\text{CH}_3 > -\text{C}_6\text{H}_5 > -\text{CH}_2\text{C}_6\text{H}_5$ , but the effect is not marked. It is apparent that the effect of a group R, where R is phenyl, a carboxyl derivative or a cationic group  $-\text{NR}'_3^+$  is greater than the effect of the group  $\text{CH}_2\text{R}$ . In view of the almost complete reversal of the influence of the phenyl group on converting methylbenzylbenzhydramine (I) to its hydrochloride the above generalization must be applied with caution to this substituent.

Dahn, Solms and Zoller<sup>9</sup> have noted a resemblance between their series of benzyl-like groups decreasing the stability of the adjacent C-N bond to hydrogenolysis, *viz.*,  $\alpha$ -menaphthyl  $>$   $\beta$ -menaphthyl  $>$  fluorenyl  $>$  benzhydryl  $>$  *p*-phenylbenzyl  $>$  benzyl, and a series obtained by Ingold and Patel<sup>12</sup> for the decreasing ease of solvolysis of the corresponding halides:  $\alpha$ -menaphthyl  $>$   $\beta$ -menaphthyl  $>$  *p*-phenylbenzyl  $>$  benzyl. At the same time the Swiss authors point out, correctly, that the influence of substituents in the aromatic nucleus as observed in these laboratories<sup>2,3</sup> is not compatible with an ionoid mechanism.<sup>13</sup> The known facts are, however, consistent with an homolytic mechanism for hydrogenolysis if the very reasonable assumption is made that steric and adsorption influences operate.

In a homolytic mechanism the critical step in the hydrogenolysis of a benzyl group from a tertiary amine would be



while for its cation



Such reactions should be markedly dependent on the stability of the  $\text{RCH}_2$  radical which should parallel closely the stability of the carbonium ion  $\text{RCH}_2^+$  except in respect to the influence of polar substituents in R. Evidence from the dissociation constants of polyarylethanes, while not directly applicable to the present argument because of steric complications, suggests that polar factors contribute little to the stability of free radicals.

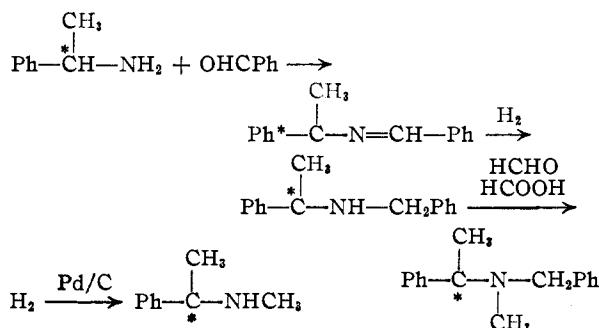
On the above basis, the stabilizing influence of substituents in the ring or the  $\alpha$ -position of a benzyl group should be due to their effect on the adsorption of the molecule or portion of the molecule on the catalytic surface. It seems fairly obvious that an  $\alpha$ -substituent might interfere sterically with

(12) C. K. Ingold and C. S. Patel, *J. Indian Chem. Soc.*, **1**, 95 (1930).

(13) There are some minor discrepancies between the above series of Ingold and Patel and similar series observed by J. F. Norris and co-workers (*THIS JOURNAL*, **50**, 1804, 1808 (1928)) and by S. Altscher, R. Baltzly and S. W. Blackman (*ibid.*, **74**, 3649 (1952)) for the solvolysis of benzhydryl chlorides (*p*-phenylbenzhydryl  $>$   $\alpha$ -( $\beta$ -menaphthyl)-benzyl  $>$   $\alpha$ -( $\alpha$ -menaphthyl)-benzyl  $>$  benzhydryl). This could be due to steric interference with resonance in the more crowded benzhydrylcarbonium ion. On this premise the series of Ingold and Patel is of more fundamental significance than that obtained by a study of the solvolysis of benzhydryl chlorides.

adsorption, but in the absence of knowledge of the geometry of the catalytic surface involved speculation as to the steric effects of ring substituents is futile. One further point which must be clarified by any satisfactory explanation of hydrogenolysis may be mentioned. This is the well known fact<sup>2,3,7-9,14</sup> that the ease of removal of a benzyl group from a nitrogen atom is greatly dependent on the presence of other substituents on this atom; thus the ease of debenzylation increases in the series:  $-\text{NH}_2 < -\text{NH}- < -\text{N}- < -\text{N} < ^+$ .

The preparation of the required tertiary amines presented little difficulty. Two general methods were employed, the choice between them being made chiefly on the availability of the required starting material. The first method (route A) involved the formation of the benzyl (or substituted benzyl)-methylamine by the application of the Wallach procedure<sup>15</sup> and the reaction of this secondary amine with the required benzyl halide. The alternative procedure (route B) consisted in the reaction of the required benzyl (or substituted benzyl)-amine with a benzaldehyde to give a Schiff base which after reduction to the corresponding secondary amine was methylated by the Clarke-Eschweiler<sup>16</sup> technique. The resolution of *dl*- $\alpha$ -phenethylmethylamine was not achieved. A sample of pure 1- $\alpha$ -phenethylmethylamine was prepared by the application of the Decker method<sup>17</sup> to the available 1- $\alpha$ -phenethylamine. Several difficulties were encountered in carrying out this synthesis which is described in detail in the Experimental section. A more elegant method of preparation of this compound now appears possible using route B above followed by a debenzylation of the resulting active methylbenzyl- $\alpha$ -phenethyl-amine. As shown in Table I (reduction 2) this debenzylation proceeds unilaterally with removal of the benzyl group.



### Experimental

All melting points are uncorrected.

**Methylbenzylbenzhydramine.**—Dahn, Solms and Zoller<sup>9</sup> prepared this compound by methylation of benzylbenzhydramine by the Clarke-Eschweiler procedure and also by benzylation of methylbenzylbenzhydramine. For the present work the amine was prepared by heating benzhydryl chloride with methylbenzylamine (2 mols) on the steam-bath for eight hours. The hydrochloride was purified by crystallization from water, m.p. 218°.

**$\alpha$ -Phenethylbenzylmethylamine Hydrochloride.**—This compound was prepared by route A.  $\alpha$ -Phenethylmethyl-

(14) L. Birkhofer and E. F. Möller, *Ber.*, **75**, 429 (1942).

(15) A. Novelli, *THIS JOURNAL*, **61**, 520 (1939).

(16) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *ibid.*, **55**, 457 (1933).

(17) H. Decker and P. Becker, *Ann.*, **395**, 362 (1913).

amine<sup>18</sup> (20 g.) and benzyl chloride (9.5 g.) were dissolved in dry ether (100 ml.) and the mixture allowed to stand at room temperature for one week. At the end of that time it was refluxed, and on cooling the secondary amine hydrochloride (3.85 g.) separated. The solution was washed with distilled water and the washings on evaporation gave a further 5 g. of the secondary amine hydrochloride. The ether solution was evaporated and the residue treated with acetic anhydride (20 ml.). After warming on the steam-bath for one hour the excess of acetic anhydride was decomposed with methanol. The solution was then dissolved in ether and the tertiary base extracted with several portions of 2 *N* hydrochloric acid. The acid solution was evaporated to dryness and the hydrochloride crystallized. It formed colorless prisms on recrystallization from ethanol-ether (11.7 g.), m.p. 162°.

*Anal.* Calcd. for  $C_{16}H_{19}N \cdot HCl$ : C, 73.4; H, 7.7. Found: C, 73.6; H, 7.8.

***dl*- $\alpha$ -Phenethyl-*p*-methylbenzylamine Hydrochloride.**—This compound was prepared by route B. *dl*- $\alpha$ -Phenethylamine (24 g.) was mixed with *p*-methylbenzaldehyde (24 g.) and the mixture heated at 100° *in vacuo* for two hours. The Schiff base was formed with the evolution of water. The *p*-methylbenzal- $\alpha$ -phenethylamine was reduced in two batches. The base (22 g.) in methanol (60 ml.) and acetic acid (10 ml.) was shaken with platinized charcoal in the presence of hydrogen. The reduction was completed rapidly. To the solution concentrated hydrochloric acid (11 ml.) was added and the solution evaporated *in vacuo*. The hydrochloride was recrystallized from ethanol-ethyl acetate several times, m.p. 199°.

*Anal.* Calcd. for  $C_{16}H_{20}NCl$ : C, 73.4; H, 7.7. Found: C, 73.6; H, 7.2.

The above hydrochloride (25 g.) was converted to the free base; this was heated on the steam-bath with formalin (10 ml. 38%) and formic acid (10 ml. 90%). Carbon dioxide was evolved; after 4 hours heating a further quantity of formalin and formic acid (5 ml. of each) was added and the heating continued for a further hour. Concentrated hydrochloric acid (15 ml.) was added and the contents evaporated *in vacuo*. The hydrochloride crystallized and, after several recrystallizations from ethanol-ether it formed colorless needles m.p. 178°. From both runs a total of 35 g. of recrystallized product was obtained.

*Anal.* Calcd. for  $C_{17}H_{22}NCl$ : C, 74.0; H, 8.0. Found: C, 73.7; H, 8.1.

***d*- $\alpha$ -Phenethyl-*p*-methylbenzylamine Hydrochloride** was prepared in exactly the same way from *d*- $\alpha$ -phenethylamine.<sup>18</sup> The *d*- $\alpha$ -phenethyl-*p*-methylbenzylamine hydrochloride melted at 167–168°.

*Anal.* Calcd. for  $C_{16}H_{20}NCl$ : C, 73.4; H, 7.7. Found: C, 73.6; H, 7.8.

**Optical Rotation.**—Five-tenths gram in 10 ml. of ethanol (95%) gave  $\alpha$  +2.68°, *l* 2 dm., *T* 31°,  $\lambda_{H\alpha}$  5461;  $[\alpha]_{5461}^{25}$  +26.8°.

The tertiary amine hydrochloride formed by methylation melted at 171°;  $[\alpha]_{5461}^{25}$  17.6° (5% in ethanol).

*Anal.* Calcd. for  $C_{17}H_{22}NHCl$ : C, 74.0; H, 8.0. Found: C, 73.9; H, 8.1.

**$\alpha$ -Phenethyl-*p*-methoxybenzylamine Hydrochloride (Route B).**— $\alpha$ -Phenethylamine (25 g.) and anisaldehyde (25 g.) were condensed to give the Schiff base as in the previous example. This on catalytic reduction gave  $\alpha$ -phenethyl-*p*-methoxybenzylamine hydrochloride (51 g.) which melted at 150–151° after recrystallization from ethanol-ether.

*Anal.* Calcd. for  $C_{16}H_{20}ONCl$ : C, 69.2; H, 7.2. Found: C, 69.1; H, 6.7.

On methylation by the Clarke–Eschweiler procedure this gave the tertiary base, the hydrochloride of which melted at 186° (37 g.). It formed colorless needles from ethanol-ether.

*Anal.* Calcd. for  $C_{17}H_{22}ONCl$ : C, 70.0; H, 7.5. Found: C, 69.8; H, 7.5.

**$\alpha$ -Phenethyl-*p*-nitrobenzylmethylamine Hydrochloride (Route A).**— $\alpha$ -Phenethylmethylamine<sup>19</sup> (27 g.) and *p*-nitrobenzyl bromide (21.6 g.) were dissolved in acetone (200 ml.).

The mixture was allowed to stand for 48 hours. An equal volume of ether was added and the secondary amine hydrochloride (18 g., theory 21.6 g.) was collected. The ethereal solution was washed with water and then extracted several times with 2 *N* hydrochloric acid. The acid extract on basification gave an oil; this after treatment with acetic anhydride in the usual manner gave the hydrochloride which after recrystallization from acetone-ether melted at 140°.

*Anal.* Calcd. for  $C_{16}H_{19}O_2N_2Cl$ : C, 62.6; H, 6.1. Found: C, 62.5; H, 6.1.

**$\alpha$ - $\beta$ -Diphenylethylbenzylmethylamine Hydrochloride (Route B).**— $\alpha$ -Aminodiphenylethane hydrochloride<sup>19</sup> (9 g.) was converted to the free base and this was heated with benzaldehyde (3.8 g.) *in vacuo*. When all the water had been expelled the benzalaminodiphenylethane solidified. This base was hydrogenated to the  $\alpha$ -benzylaminodiphenylethane in the usual manner and the hydrochloride of this compound after recrystallization from ethanol formed needles, m.p. 248°.

*Anal.* Calcd. for  $C_{21}H_{22}NCl$ : C, 77.9; H, 6.8. Found: C, 78.1; H, 6.6.

The above hydrochloride was converted to the free base and this was reacted with formalin (7 ml., 37%) and formic acid (7 ml., 98%) under the usual Clarke–Eschweiler conditions. When the reaction was complete the mixture was cooled, treated with concentrated hydrochloric acid (20 ml.) and evaporated. The hydrochloride crystallized at once; on recrystallization from ethanol it formed needles, m.p. 223° (7.0 g.).

*Anal.* Calcd. for  $C_{22}H_{24}NCl$ : C, 78.3; H, 7.1. Found: C, 78.0; H, 7.3.

**1- $\alpha$ -Phenethylmethylamine Hydrochloride.**—1- $\alpha$ -Phenethylamine<sup>18</sup> (10 g.,  $[\alpha]_{5461}^{20}$  –37.8°) was added to benzaldehyde (9 g.) in a 250-ml. centrifuge cup and the resultant water removed *in vacuo*. Methyl iodide (12 g.) was then added and the container closed and allowed to stand for one month at 40–50°. The mixture became thick but did not crystallize; it was thereupon dissolved in 95% ethanol and the solution boiled. On cooling, the base hydriodide could not be obtained crystalline. The base from the hydriodide was converted to the benzoyl derivative.<sup>20</sup> The first solid fractions proved to be benzoyl 1- $\alpha$ -phenethylamine. The remaining benzoyl derivatives were distilled b.p. ca. 125° (bath temperature) (0.03 mm.). Two fractions A and B (7 g. each) were collected; fraction A was redistilled to give a further two fractions A' and B'. Fraction B' resembled B in appearance and from these two a solid (3 g.), m.p. 56.5–57.5, was isolated. Attempted hydrolysis of this solid with alcoholic potassium hydroxide yielded a base, whose hydrochloride melted at 211.5–213°, in very small quantity. The base was liberated from the amide more satisfactorily by refluxing with ethylmagnesium bromide in ether. The total basic fraction was converted to the hydrochloride, and the hydrochloride was divided into two fractions; a least soluble fraction of m.p. 214° (0.5 g.) and a second fraction (0.3 g.) of m.p. 213°. The second fraction appeared to be pure 1- $\alpha$ -phenethylmethylamine hydrochloride.

*Anal.* Calcd. for  $C_9H_{14}NCl$ : C, 62.9; H, 8.2. Found: C, 62.9; H, 8.2.

**Optical Rotation.**—In ethanol in 5% solution  $[\alpha]_{5461}^{25}$  –29.7°, in 2.5% solution  $[\alpha]_{5461}^{25}$  –30.0°.

**Hydrogenolyses.**—The methods employed have been described in our earlier papers.<sup>2,3</sup> Ethyl benzoylacetate in methanol containing a trace of hydrogen chloride absorbed one mol of hydrogen very rapidly, the second rather slowly. The product was identified as hydrocinnaamic acid hydrazide. Ethyl nicotinoylacetate has been reduced to  $\beta$ -(3-pyridyl)propionic ester by palladized barium sulfate in acetic acid.<sup>21</sup> Similar reductions in ethanol in the presence of neutralizing

(19) R. Leuckart and H. Janssen, *Ber.*, **22**, 1409 (1889).

(20) The advantage of the Decker method<sup>17</sup> rests largely on the formation of a crystalline Schiff base methiodide that can be purified by washing with dry benzene and, after hydrolysis, gives substantially pure secondary base hydriodide. Since in the present example the Schiff base methiodide was not obtained in a crystalline state and the secondary base contained the impurities usually removed at this stage, it was possible to purify it only by the rather laborious benzoylation procedure described above.

(21) E. Graef, J. M. Fredericksen and A. Burger, *J. Org. Chem.*, **11**, 257 (1946).

(18) A. W. Ingersoll, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 506.

quantities of hydrogen chloride or of glacial acetic acid were found to proceed rather slowly but with the same result as previously reported. In the absence of added acid the reduction also proceeded to completion, although the catalyst was poisoned toward reduction of cyclohexene.

The reduction of  $\beta$ -dimethylaminopropiophenone hydrochloride proceeded at a moderate rate. The  $\gamma$ -phenylpropylmethylamine hydrochloride was rather hygroscopic and was converted to the chloroplatinate<sup>22</sup> for complete identification.

Concerning the competitive hydrogenolyses whose results are shown in Table I, only a few general remarks are necessary. In most cases the working up was conventional. The notations in the last column: > 90% or > 80% indicate that in those experiments 90 or 80%, respectively, of the cleavage product was obtained pure without unusual precautions. Reduction 3, which was quite slow, was run at about 40°.

In reduction 2a, after removal of the catalyst (through a filter-tube) the solvent was evaporated *in vacuo* and the rotation was determined on 0.5 g. of the total residue, made up to 10 cc. with alcohol:  $[\alpha]_{D}^{24.5461} +12.5^\circ$ . This indicates 42% of the optically active amine. In practice it is perhaps safer to give this as 40–45% since the solution was not quite colorless and the error in reading  $\alpha$  could have been as much as 0.05° (as against  $\pm 0.01^\circ$  with the pure hydrochlorides).

The solution from reduction 4 (15 mmoles of substrate) was evaporated *in vacuo* and the residual lavender sirup was partitioned between water and ether. The ethereal layer was evaporated on the steam-bath and the residue was digested with 3 cc. of acetic anhydride. On dilution with water there was obtained 1.8 g. of *p*-acetotoluidide. The aqueous layer was acidified with hydrochloric acid, evaporated *in vacuo* and crystallized fractionally from ethanol-ethyl acetate-ether mixtures. The least soluble material (0.2 g.) was identified as *p*-toluidine hydrochloride. From the later fractions, 1.9 g. of pure *dl*- $\alpha$ -phenethylmethylamine hydrochloride (11 mmoles) was obtained.

The examination of the products of reductions 5 and 5a deserves detailed attention in view of the surprising results. Reduction 5 was performed twice, the second time after correspondence with Professor Dahn. Twenty mmoles (6.5 g.) of benzylmethylbenzhydramine hydrochloride was reduced rather slowly, the calculated amount of hydrogen being absorbed. After removal from the catalyst, the solvent (methanol) was distilled off through a fractionating column at atmospheric pressure and the residue was partitioned between ether and water. The ethereal layer was dried briefly over a little calcium chloride and evaporated on the steam-bath. The residue weighed 1.2 g. Diphenylmethane was estimated by nitration (to tetranitrodiphenylmethane) as being 0.9 g. This nitration is not quite quantitative. Estimates were made on the basis of yields obtained by the nitration of authentic diphenylmethane.

The aqueous layer was evaporated *in vacuo* on the steam-bath; the residue weighed 4 g. It was dissolved in 10 cc. of

water and allowed to stand overnight; no solid separated. The solution was transferred to a separatory funnel, diluted to about 30 cc., overlaid with ether and basified by addition of standard alkali with extraction of liberated base after each addition. The fractions of base were expected to contain 8, 4, 4 and 4 mmoles, respectively. Each fraction of base, in ether, was dried over potassium carbonate and acidified by addition of ethanolic hydrogen chloride. Fractions I and II weighed 1.9 and 1 g., respectively, and melted at 217–218°. Fraction III weighed 0.5 g. and melted at 169–175° and fraction IV weighed 0.3 g. and melted at 179–180°. Fraction IV was pure benzylmethylamine hydrochloride. Further fractionation of fraction III and of the mother liquors of the other three fractions afforded 0.3 g. more of benzhydramine hydrochloride, along with 0.3 g. of pure and about 0.2 g. of somewhat impure benzylmethylamine hydrochloride (these further fractionations involved repartitioning as well as crystallization).

In our hands, benzhydramine hydrochloride usually separated from alcohol-ether mixtures as elongated prisms or needles that melted at 218°. A sample of this material, after standing about a year, melted at 238° as usually reported (*cf.* ref. 8 and Table I, note b). It was later found that when these prisms, m.p., 218°, were allowed to stand in contact with their mother liquors (12–40 hours) they tended to dissolve and be replaced by more stubby and massive crystals that melted at 238°.

The fractionation with reduction 5a was along similar lines but was modified so as to isolate the small amount of benzhydramine present. Dahn and his co-workers had sought this product in the least soluble fraction of hydrochlorides from their reductions. We believed this to be an unsound method for crystallizations from ethanol-ether mixtures.

The initial separation between neutral and basic material in this case was the same as with reduction 5. The amount of diphenylmethane was estimated as 2.1 g. (60%). The aqueous layer was overlaid with ether and 1 cc. of 2.2 *N* sodium hydroxide solution was added. After shaking, the aqueous layer was withdrawn and the ethereal layer was washed with water to which 2 cc. of 0.1 *N* hydrochloric acid had been added. The ethereal layer was then dried over potassium carbonate and acidified with ethanolic hydrogen chloride. The crystals that separated were pure benzhydramine hydrochloride; this fraction was 10% of the total bases. Repetition of this operation on the ethereal layer gave a second 10% portion of bases whose hydrochloride was oily and, on washing with acetone, gave crystals of benzylmethylamine hydrochloride. The rest of the basic material was also benzylmethylamine. The cleavage had thus given more than 10% and less than 20% of benzhydramine.

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(22) H. Emde, *Ann.*, **391**, 94 (1912).