

2. The acid *n*-amyl and *n*-hexyl esters of 3-nitrophthalic acid have been described.

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

## THE PREPARATION OF SOME PRIMARY AMINES BY THE CATALYTIC REDUCTION OF NITRILES

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The preparation of primary amines by the reduction of nitriles with the usual chemical reagents is frequently unsatisfactory. The catalytic method has been studied by several investigators<sup>1</sup> with diverse results. Apparently the course of the reaction is greatly influenced by the nature of the nitrile, the catalyst, the solvent, the conditions of temperature and pressure, etc. Secondary amines are usually formed as well as primary, and the former may frequently constitute the chief reaction products.

The platinum oxide catalyst described and extensively applied by Adams<sup>2</sup> and his students has been found extremely effective in a variety of reductions. There is here presented a brief study of the behavior of this catalyst in the reduction of certain nitriles. Especial attention was directed toward elimination of the formation of secondary amines, and the reactions were carried out on such a scale that the results might be of some practical use in synthetic work.

Preliminary small-scale experiments showed that the reduction of benzyl cyanide proceeded at a practicable rate in glacial acetic acid, acetic anhydride, and absolute alcohol, but only very slowly in absolute ethyl ether. It was then established that reduction of benzonitrile and

TABLE I  
RELATIVE AMOUNTS OF PRIMARY AND SECONDARY AMINES FORMED IN ALCOHOL AND ACETIC ACID SOLUTIONS

Nitrile	Solvent	% Primary amine	% Secondary amine
Benzonitrile	Alcohol	21	79
Benzonitrile	Acetic acid	62	38
<i>p</i> -Tolunitrile	Alcohol	33	67
<i>p</i> -Tolunitrile	Acetic acid	4	84

<sup>1</sup> (a) Rupe and Gisiger, *Helvetica Chim. Acta*, **8**, 338 (1925). (b) v. Braun, Blessing and Zobel, *Ber.*, **56**, 1988 (1923). (c) Rosenmund and Pfankuch, *Ber.*, **56**, 2258 (1923). (d) Grignard and Escourrou, *Compt. rend.*, **180**, 1883 (1925); and other references in these papers.

<sup>2</sup> THIS JOURNAL, (a) **44**, 1397 (1922); (b) **45**, 1071, (c) 2171, (d) 3029 (1923); (e) **46**, 1675, (f) 1684 (1924); (g) **47**, 1047, (h) 1098, (i) 1147 (1925).

*p*-tolunitrile in absolute alcohol or glacial acetic acid results in the formation of considerable amounts of secondary amine.<sup>3</sup>

The approximate compositions of the total free organic bases isolated from the reduction mixtures produced in these solvents are given in Table I.

Explanations<sup>4</sup> of the commonly observed formation of secondary amines in the catalytic reduction of nitriles usually involve the assumption of the hydrolysis of an intermediate imine, or the condensation, under the influence of the catalyst, of a molecule of the primary amine either with a molecule of the imine or with another molecule of the primary amine. The use of acetic anhydride as a solvent should avoid the formation of secondary amine by any of these mechanisms, for hydrolysis would be impossible in such a solution, while any primary amine would be quickly acylated and so protected against further reaction.

This expectation was fully realized. The reduction of benzonitrile, *o*- and *p*-tolunitriles and benzyl cyanide proceeds smoothly in acetic anhydride solution with the formation of the acetyl derivatives of the corresponding primary amines. Secondary amines or their acetyl derivatives are absent, and hydrolysis of the reaction products by means of concd. hydrochloric acid gives pure primary amines in good yields.<sup>5</sup>

The reduction of *p*-tolunitrile is especially successful. Using 0.25 g. of catalyst, 0.2 mole (23.4 g.) of the nitrile absorbs somewhat more than the calculated amount of hydrogen in five to eight hours. The platinum is then readily filtered from the water-white solution and, on addition of alkali in the cold, the crystalline acetyl derivative of *p*-methylbenzylamine separates in 88% yield. The crude product melts within 1° of the true melting point of acetyl *p*-methylbenzylamine, and 3° higher than the previously recorded melting point for that substance.

Benzonitrile and *o*-tolunitrile are also reduced quite readily, but the reduction of benzyl cyanide is slower and requires the use of a somewhat

<sup>3</sup> Rosenmund and Pfankuch (Ref. 1 c), using palladium barium sulfate catalyst, reduced some nitriles and oxime acetates in acetic acid solution (in some cases with the addition of mineral acid) to primary amines. The amounts of material reduced were, in the examples cited, very small (less than 0.5 g.), and the amines were isolated as the hydrochlorides.

<sup>4</sup> Paal and Gerum, *Ber.*, **42**, 1553 (1909). Rupe and Glenz, *Helvetica Chim. Acta*, **5**, 937 (1922). v. Braun, Blessing and Zobel, *Ber.*, **56**, 1988 (1923). Gulewitsch, *Ber.*, **57**, 1645 (1924). Rosenmund and Jordan, *Ber.*, **58**, 51 (1925).

<sup>5</sup> Although these amides are readily hydrolyzed by refluxing with concd. hydrochloric acid, acetyl-benzylamine (the only one tested in this respect) is remarkably stable toward alkali. A sample of this substance was hydrolyzed only to the extent of about 20% after boiling for 13 hours with 40% sodium hydroxide solution. In this connection it is interesting to note that Strakosch, who first prepared acetyl benzylamine [*Ber.*, **5**, 697 (1872)] by the action of benzyl chloride on acetamide, claimed for it a remarkable stability toward acid and alkali. Rudolph later showed [*Ber.*, **12**, 1297 (1879)] that it could be hydrolyzed by alcoholic alkali,

larger amount of catalyst. Preliminary experiments on trimethylene cyanide, furonitrile and imidazole-acetonitrile showed that these substances are reduced still more slowly, so that the range of applicability of the method here described is, in its present form, somewhat circumscribed. The reduction products of these nitriles are of especial interest, and it is hoped that further study may discover more favorable conditions for their formation. *p*-Tolunitrile is also reduced without difficulty in *n*-butyric anhydride solution with the formation of *n*-butyryl-*p*-methylbenzylamine, so that the reduction of nitriles in the presence of acid anhydrides will, perhaps, be found a very convenient if not a perfectly general method for bringing about, in a single step, the transformation:  $\text{RCN} \rightarrow \text{RCH}_2\text{NHCOR}'$ .

Although no evidence of the presence of secondary amines was found in the acetic anhydride reductions, the yield of pure primary amine actually isolated (based on the nitrile used) fell, in one instance, as low as 63%, and never rose above 87%. It was found that the mechanical losses in the hydrolysis of small amounts of amide and isolation of the amine amounted to about 12% (amines of this type distil to a considerable extent with ether). The hydrogen is, of course, the limiting factor in determining the theoretical yield, regardless of the amount used, and assuming that each mole of hydrogen in excess of two moles causes the destruction of one mole of amide, the average yield of acetyl-*p*-methylbenzylamine in five experiments was 98% of the calculated amount. This indicates that the amount of any side reactions must have been very small. On the other hand some side reaction occurred, for the odor of unchanged nitrile was usually apparent even after more than the calculated amount of hydrogen had been absorbed and, in the reduction of benzonitrile, the addition of alkali caused the formation of considerable amounts of ammonia, while evidence was found of the presence of toluene in the indifferent fraction. The side reaction which occurs is, then, probably the further reduction of the acetyl derivative of the primary amine to the hydrocarbon and acetamide.

The apparatus and general technique of the method used here have already been described.<sup>2c,2d</sup> The catalyst was prepared from especially purified chloroplatinic acid, and the reductions were carried out with an initial hydrogen pressure of 3 to 4 atmospheres.

The following observations may be of some value in working with nitriles. The speed of the reduction increases very rapidly with rise in temperature. So also does the tendency for the catalyst to become poisoned. Hence at higher temperatures (50–100°) the rate of reduction is at first extremely rapid; then quite suddenly and, when small amounts of catalyst are used, before the reaction is complete, the reduction stops entirely. The optimum temperature will depend not only

upon the nitrile, but also on the amount of catalyst used, the solvent ratio, etc. Probably in most cases it is 10–30 degrees above room temperature. The reductions described here were, for the most part, carried out at room temperature. Shaking with air does not reactivate the catalyst, nor does the addition of iron salt protect it against the poisoning action of the reaction mixture. It was found desirable, frequently, to evacuate the hydrogen reservoir or to wash it out with air to prevent the accumulation of poisonous impurities. From the standpoint of catalyst economy it was also frequently desirable to add the catalyst in two portions, the second after the reaction had begun to slow down.

In connection with this work it was observed that the acetyl derivatives of all the primary amines here described (benzylamine, *o*- and *p*-methylbenzylamines and  $\beta$ -phenethylamine) are quite soluble in cold dilute hydrochloric acid,<sup>6</sup> and are precipitated unchanged on the addition of alkali. This led to the preparation of other acyl derivatives of these amines of which the following appear to be new. The acid solubility of the acetyl derivatives might, perhaps, have been predicted from the strongly basic character of the amines, but it does not appear to have been recorded by previous investigators. The strongly basic character of the amines also finds expression in the fact that the aromatic sulfonyl derivatives, are insoluble or only slightly soluble in cold dilute alkali solutions. On the other hand, the phenyl carbamides, unlike the acetyl derivatives, are insoluble in dilute acid. The properties and especially

TABLE II

## ANALYSES AND MELTING POINTS OF SULFONAMIDES AND PHENYLCARBAMIDES

Substance	Analysis, % N		M. p. (cor.) C.
	Calcd.	Found	
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHCONHC <sub>6</sub> H <sub>5</sub>	11.66	11.70	188–188.2
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> - <i>p</i>	5.09	5.11	94.7–95.5
<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Br- <i>p</i>	4.12	4.13	126.5–127.5
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHCONHC <sub>6</sub> H <sub>5</sub>	11.66	11.56	167.5–168
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	5.36	5.49	128.3–129.1
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>3</sub> - <i>p</i>	5.09	5.06	118.7–119.2
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Br- <i>p</i>	4.12	4.17	106.5–107
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NHSO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> Br- <i>p</i>	4.12	3.98	88.5–89.5
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CH <sub>2</sub> NHCONHC <sub>6</sub> H <sub>5</sub> <sup>a</sup>	11.66	11.60	153.5–154.5

<sup>a</sup> Previously prepared from phenethyl-isocyanate and aniline by Forster and Stötter [*J. Chem. Soc.*, **99**, 1338 (1911)] who state that it melts somewhat indefinitely at 148°.

<sup>6</sup> Using 0.1g. samples of the amides and successive portions of approximately 4 N HCl, the following observations were made: acetyl-benzylamine was rapidly and completely dissolved by 0.5 cc. of acid; acetyl- $\beta$ -phenethylamine, rapidly dissolved by 0.3 cc. of acid; acetyl-*o*-methylbenzylamine, rapidly dissolved by 1 cc. of acid; acetyl-*p*-methylbenzylamine, slowly dissolved by 2.5 cc. of acid. On warming slightly it dissolved rapidly in a smaller amount of acid.

the basic strength of the acyl derivatives of these amines are to be studied in more detail. The sulfonyl derivatives were prepared by the action of the acid chloride on the amine in the presence of an excess of 5 *N* sodium hydroxide solution. They separated from such a solution without the addition of acid, although dilution was sometimes necessary to complete the precipitation. The phenyl carbamides were prepared by the action of the amines on phenylisocyanate.

**Reduction of *p*-Tolunitrile in Acetic Anhydride Solution.**—A mixture of 23.4 g. (0.2 mole) of *p*-tolunitrile, 0.24 g. of catalyst, and 60 cc. of acetic anhydride was shaken with hydrogen under pressure of about three atmospheres. Hydrogen was rapidly absorbed, and after about four hours, crystals began to separate in the flask. The bottle was opened and 25 cc. of acetic anhydride and 50 cc. of acetic acid were added to bring the crystals into solution, and the reduction was continued. About 6% more than the calculated amount of hydrogen was absorbed in  $5\frac{1}{3}$  hours. (In subsequent runs the time was somewhat longer.) The platinum was filtered off through an asbestos pad, and the filtrate decomposed with ice and aqueous sodium hydroxide. The crystalline acetyl derivative was filtered off and dried in a vacuum at 85°. The yield was 28.7 g. (88%) of a solid<sup>7</sup> melting at 110–111° (corr.). It was crystallized from dil. alcohol, and from a mixture of benzene and ligroin to a constant melting point, 111–112°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>ON: C, 73.57; H, 8.05. Found: C, 73.37; H, 8.19.

The substance is very soluble in warm 20–30% hydrochloric acid, and when such a solution is refluxed and then cooled, the hydrochloride of *p*-methylbenzylamine separates; m. p.,<sup>8</sup> 234–234.5°.

*Anal.* (dried at 75°): Calcd. for C<sub>8</sub>H<sub>12</sub>NCl $\frac{1}{2}$ H<sub>2</sub>O: Cl, 21.29; H<sub>2</sub>O, 5.41. Found: Cl, 21.12, 21.16; H<sub>2</sub>O, 5.44.

Hydrolysis of the recrystallized acetyl derivative yields very pure *p*-methylbenzylamine. When 23.4 g. of acetyl derivative was hydrolyzed with concd. hydrochloric acid, made alkaline, extracted with ether, dried and distilled, it gave 15.4 g. (88.7%) of water-white amine; b. p., 108° (54 mm.) to 106° (50.5 mm.); neutral equivalent: calcd., 121.1; found: 120.5, 120.6.

**Reduction of *p*-Tolunitrile in Glacial Acetic Acid.**—A mixture of 46.8 g. (0.4 mole) of nitrile, 80 cc. of acetic acid and 0.25 g. of catalyst absorbed 45% of the calculated amount of hydrogen in 2 $\frac{1}{4}$  hours; 0.2 g. more of catalyst was then added. Toward the end of the reduction the contents of the reaction bottle became very thick with the separation of crystals, and an unsuccessful attempt was made to dissolve these by the addition of 40 cc. more of glacial acetic acid. At the end of 6 $\frac{1}{2}$  hours, 103% of the calculated amount of hydrogen had been absorbed. The reaction mixture was treated with a large excess of aqueous sodium hydroxide, boiled under a reflux condenser to destroy unchanged nitrile, extracted, etc. Distillation gave 1.5 g. of a substance boiling at 86–92° (18 mm.) (primary amine) and 32 g. of another boiling at 202–210° (18 mm.) (chiefly at 202–204°). There was also a residue of 4.4 g. which boiled continuously from 200° to 254° (8 mm.) and which may have contained some tertiary amine. The second fraction was identified as di(*p*-methylbenzyl)amine. It crystallized almost completely at room temperature, and when a small amount of liquid was poured off and the crystals melted, they were found to freeze at 33.5° (corr.).<sup>9</sup> The rapidity of the

<sup>7</sup> Lustig [*Ber.*, **28**, 2988 (1895)] gives acetyl-*p*-methylbenzylamine, m. p. 107–108°

<sup>8</sup> Bamberger and Lodter [*Ber.*, **20**, 1710 (1887)] give m. p. 234.5–235°.

<sup>9</sup> Curtius [*J. prakt. Chem.*, [2] **62**, 100 (1900)] gives m. p. 32.5°.

reduction and the yield (71%) commend this as a method for the preparation of this secondary amine.

**Reduction of *p*-Tolunitrile in Absolute Ethyl Alcohol.**—A solution of 23.4 g. of nitrile in 80 cc. of absolute ethyl alcohol with 0.55 g. of catalyst, absorbed 101% of the calculated amount of hydrogen in 10 hours. Distillation gave 6.3 g. of impure *p*-methylbenzylamine, and 12.7 g. of di(*p*-methylbenzyl)amine.

**Reduction of *p*-Tolunitrile in *n*-Butyric Anhydride.**—A solution of 11.7 g. of nitrile in 34 g. of butyric anhydride with 0.2 g. of catalyst absorbed the calculated amount of hydrogen in 8½ hours. Addition of alkali in the cold caused the separation of pure white, waxy crystals. Recrystallization from ether and ligroin gave 14.2 g. (74%) of *n*-butyryl-*p*-methylbenzylamine; m. p., 71–72°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>17</sub>ON: N, 7.33%. Found: 7.38, 7.50.

**Reduction of Benzonitrile in Acetic Anhydride Solution.**—A solution of 20.6 g. (0.2 mole) of the nitrile in 50 cc. of acetic anhydride absorbed 106% of the calculated amount of hydrogen in 6⅓ hours. The catalyst was added in two portions, 0.3 g. at the start and 0.15 g. at the middle of the reduction. After the platinum had been removed, the clear liquid was treated with ice and alkali, when the acetyl derivative of benzylamine separated and was filtered off. It remained sticky even after being dried for one month over sulfuric acid and still had an odor of unchanged nitrile; yield, 25.2 g. On recrystallization it melted<sup>10</sup> at 60.4–61.4°. It is very soluble in cold dil. hydrochloric acid.

In a similar experiment 41.2 g. of nitrile (0.4 mole) was reduced. The acetyl derivative was extracted with ether, hydrolyzed, etc., and gave on distillation 29.7 g. (69%) of benzylamine; b. p., 84–85° at 24.5 mm.

In another similar experiment the ethereal extract from the reduction mixture (after the addition of excess aqueous alkali in the cold) was extracted with dil. hydrochloric acid to separate the basic material (acetylbenzylamine) from the indifferent material, and the ethereal solution was distilled. About 0.3 g. of a liquid boiling at 110–116° and having the odor of toluene was isolated.

**Reduction of Benzonitrile in Glacial Acetic Acid.**—A solution of 41.2 g. (0.4 mole) of nitrile in 80 cc. of acetic acid with 0.5 g. of catalyst absorbed 105% of the calculated amount of hydrogen in seven hours. The reaction mixture was extremely viscous and filtration of the platinum very slow. The reaction product was boiled with an excess of aqueous sodium hydroxide. Distillation of the extract gave 20 g. of benzylamine, boiling at 75–78.5° (15 mm.) and 12.4 g. of dibenzylamine boiling at 160–170° (15 mm.).

**Reduction of Benzonitrile in Absolute Ethyl Alcohol.**—The reduction of 41.2 g. of nitrile in 130 cc. of alcohol required 21 hours and the use of 0.8 g. of catalyst. Much ammonia was formed. Distillation gave 6.8 g. of a liquid boiling from 82.5° (15 mm.) to 81° (13 mm.) and 26 g. of dibenzylamine boiling at 133–135° at 2 mm. The first fraction had a strong odor of nitrile. Titration indicated that it contained about 73% of benzylamine.

**Reduction of *o*-Tolunitrile.**—With 0.5 g. of catalyst, 23.4 g. of nitrile in 60 cc. of acetic anhydride was reduced in 10½ hours. The acetyl derivative of *o*-methylbenzylamine was isolated in the usual way. The crude substance was very sticky after being dried over sulfuric acid; yield, 30.7 g. Recrystallized from benzene and ligroin, and from alcohol it melted<sup>11</sup> at 76–76.5°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>ON: N, 8.58%. Found: 8.48.

Hydrolysis in the usual manner yielded the primary amine.

<sup>10</sup> Amsel and Hofmann [*Ber.*, **19**, 1286 (1886)] give m. p. 60–61°. Rügheimer and Ritter [*Ber.*, **45**, 1335 (1912)], 62–66°.

<sup>11</sup> Strassmann [*Ber.*, **21**, 578 (1888)] gives m. p. 69°.

**Reduction of Benzyl Cyanide.**—A solution of 23.4 g. (0.2 mole) of nitrile in 50 cc. of acetic anhydride absorbed 115% of the calculated amount of hydrogen in 22 hours when 1.2 g. of catalyst added in two portions was used. The product was hydrolyzed with acid, the acid solution extracted to remove non-basic material, and the  $\beta$ -phenethylamine isolated in the usual way. The yield was 15.2 g. (63%) of a product boiling from 82.5° to 83° (14 mm.).

In the reduction of small amounts of nitrile the acetyl derivative of the amine is best isolated by extraction with dil. hydrochloric acid. Thus 1.92 g. of nitrile in 20 cc. of acetic anhydride with 0.15 g. of catalyst was reduced in five hours with hydrogen at atmospheric pressure. The platinum was filtered off, the filtrate treated with aqueous sodium hydroxide and extracted with ether. The ethereal layer was extracted with dil. hydrochloric acid, the acid layer was made alkaline, and extracted with ether. The residue from the evaporation of the ether was crystalline acetyl  $\beta$ -phenethylamine; yield 1.61 g. or 62%. On recrystallization it melted<sup>12</sup> at 51–52°.

### Summary

Although the reduction of nitriles in the usual solvents commonly leads to a mixture of primary and secondary amines, it is shown that (when the platinum oxide catalyst of Adams is used) *o*- and *p*-tolunitriles, benzonitrile and benzyl cyanide are smoothly reduced in acetic anhydride solution with the formation of the acetyl derivatives of the corresponding primary amines. Secondary amines or their acetyl derivatives are absent. *p*-Tolunitrile is reduced in butyric anhydride with the formation of *n*-butyryl-*p*-methylbenzylamine. A method is thus provided for conveniently bringing about in a single step the transformations,  $\text{RCN} \rightarrow \text{RCH}_2\text{NHCOR}'$ . The acetyl derivatives are readily hydrolyzed by concd. hydrochloric acid with the formation of the pure primary amines in good yields.

Some new acyl derivatives of these amines are described, and it is pointed out that the acetyl derivatives are readily soluble in cold dil. hydrochloric acid and are precipitated unchanged on the addition of alkali, while the aromatic sulfonyl derivatives are only slightly soluble in cold alkali.

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<sup>12</sup> Michaelis and Linow [*Ber.*, **26**, 2167 (1893)] give m. p. 51°.