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## Catalytic Reduction of Mandelonitriles

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In an attempt to simplify the preparation of  $\beta$ -phenylethylamines, the catalytic reduction of mandelonitriles was investigated. Some previous work in this direction has been cited by Hartung.<sup>1</sup> Little seems to have been done at moderate pressures and at room temperature. Kindler<sup>2</sup> reports that the reaction fails, and<sup>3</sup> that acylated nitriles reduce badly, giving poor yields of the  $\beta$ -phenylethylamines. Paal and Gerum,<sup>4</sup> in earlier work, reduced mandelonitrile, using palladium, to benzyl alcohol, benzylamine, dibenzylamine and ammonia. Hartung<sup>1</sup> gave details for the reduction of mandelonitrile to  $\beta$ -phenylethylamine and noted the non-production of  $\beta$ -hydroxy- $\beta$ -phenylethylamine. He used palladium charcoal as catalyst and alcoholic hydrogen chloride as solvent. The Adams catalyst (platinum oxide) and the usual apparatus (Burgess-Parr) offer a simple and expedient method of reduction and were used by the present author to reduce a number of mandelonitriles. In the presence of a slight excess of concentrated hydrochloric acid, the nitrile, in alcoholic solution, is smoothly reduced to the corresponding  $\beta$ -phenylethylamine or  $\beta$ -hydroxy- $\beta$ -phenylethylamine, which one being determined by the starting material. The reaction is complex, and attention was directed solely to the isolation, as hydrochloride, of the amine. Although some of the yields are not altogether satisfactory, the expediency of the method makes it convenient for the preparation of certain of the  $\beta$ -phenylethylamines. Of the nitriles examined, those with ortho substituents gave the  $\beta$ -hydroxy- $\beta$ -phenylethylamine, the others giving the  $\beta$ -phenylethylamine. No meta-substituted nitriles were prepared in a state of sufficient purity for reduction. Kindler<sup>5</sup> has recently discussed the mechanism of the production of amines by reduction.

Three carbethoxymandelonitriles and one carbomethoxymandelonitrile were also reduced under the conditions given above. All four gave the corresponding  $\beta$ -phenylethylamines, showing, in the case of the *o*-chloro compounds at any rate, that more than a simple hydrolysis is involved, since the non-acylated and the acylated mandelonitriles give different products.

The *p*-nitrobenzoyl derivatives were prepared for the better characterizing of the amines, particularly as the melting points of the hydrochlorides are not always sharp.

- (1) Hartung, *THIS JOURNAL*, **50**, 3370 (1928).
- (2) Kindler, *Arch. Pharm.*, **265**, 389 (1927).
- (3) Kindler, *ibid.*, **269**, 70 (1931).
- (4) Paal and Gerum, *Ber.*, **42**, 1558 (1909).
- (5) Kindler, *Ann.*, **485**, 113 (1931).

## Experimental

The general method used was to dissolve 0.05 mole of the nitrile or acylated nitrile in 45 cc. of alcohol, and after adding 5.0 cc. of concentrated hydrochloric acid (1.2 moles) to reduce the solution, at room temperature, with platinum oxide and hydrogen. The initial pressure was 50 lb. The amount of catalyst used was between 0.3 and 1.0 g., the larger amount being used on the slower reductions. The time required for reduction was usually two hours or less, but occasionally eight to ten hours were necessary. The theoretical amount of hydrogen was rarely taken up, the reduction usually stopping considerably short of the end-point. It is essential that the starting material be pure.

The reaction mixtures were worked up by filtering off the catalyst and evaporating the filtrate to dryness under reduced pressure. The residue was then dissolved in absolute alcohol and absolute ether added to incipient precipitation. On standing in the cold the hydrochloride crystallized out and was filtered off, washed with ether, and dried *in vacuo*. The yields are recorded for material of this purity. There is considerable loss on subsequent recrystallizations owing to the unselective nature of the solvent used (alcohol-ether mixture). For practical purposes, it would be preferable, in most cases, to isolate the free amine directly from the reduction mixture.

For identification, the product was repeatedly recrystallized from alcohol-ether mixture, or in some cases from alcohol, until pure. The hydrochloride was analyzed and converted into the *p*-nitrobenzoyl derivative of the amine, which was also analyzed. In a number of cases comparison was made with authentic compounds and mixed melting point determinations carried out. The validity of the latter method is sometimes open to doubt when used with hydrochlorides as some of these have unsharp melting points (*e. g.*, homoanisylamine hydrochloride).

**Mandelonitriles.**—Three methods were used to prepare the nitriles. As a rule, the nitrile is only obtainable in quantity by one of the techniques, which is selected by trial. (1) A method similar to that of McCombie and Parry<sup>6</sup> was employed, but, although occasionally giving good yields of pure material, it was erratic. (2) Anhydrous hydrogen cyanide, in the presence of calcium oxide, was used, after the method of Bigelow, Jenkins and Buck.<sup>7</sup> (3) The bisulfite compound of the aldehyde was treated with potassium cyanide solution, in a manner similar to that of Kostanecki and Lampe.<sup>8</sup>

In all cases the crude product was extracted with ether, and washed (each washing being repeated once) with water, sodium bisulfite solution, water, sodium bicarbonate solution, and finally water. The ether solution was then dried over anhydrous sodium sulfate and the ether removed as completely as possible under reduced pressure at 25–30°. The resultant oil solidified on standing in the refrigerator and the solid was then ground with petroleum ether (b. p. 30–60°), filtered off, washed with petroleum ether

TABLE I  
MANDELONITRILES

No.	Nitrile	Prepn. method	Yield, % pure	Color	Appearance
1	<i>o</i> -Methoxy- <sup>8</sup>	(1) 3	43 (1) 65 (3)	White	Aggregates of tiny rhombs
2	<i>o</i> -Chloro-	1	73	Almost white	Small jagged needles
3	2,3-Dimethoxy-	1	54	Faint buff	Glittering broken plates
4	<i>p</i> -Methoxy- <sup>6</sup>	(1) 3	62	Faint yellow	Glittering thin needle prisms
5	3,4-Dimethoxy- <sup>6</sup>	1, 2	22 (1) 78 (2)	Faint cream	Tiny nodules
6	<i>p</i> -Chloro-	1	81	Faint yellow	Glittering long prisms

(6) McCombie and Parry, *J. Chem. Soc.*, **95**, 586 (1909).

(7) Bigelow, Jenkins and Buck, *THIS JOURNAL*, **52**, 5201 (1930).

(8) Kostanecki and Lampe, *Ber.*, **42**, 828 (1909); *cf.* German Patent 85,230.



TABLE III  
HYDROCHLORIDES OF  $\beta$ -PHENYLETHYLAMINES AND  $\beta$ -HYDROXY- $\beta$ -PHENYLETHYLAMINES

$\beta$ -Phenylethylamine	Nitrile reduced	Yield, %	M. p., °C.	Appearance	Analysis			
					Calcd.		Found	
					C	H	C	H
<i>o</i> -Methoxy- $\beta$ -hydroxy-	1	59	184	Tiny thin plates	53.05	6.93	53.22	6.97
<i>o</i> -Chloro- $\beta$ -hydroxy-	2	41	197	Crusts of broken prisms	46.15	5.33	46.32	5.61
2,3-Dimethoxy- $\beta$ -hydroxy-	3	23.5	134	Tiny jagged plates	51.37	6.90	51.52	6.82
<i>o</i> -Chloro-	11	94	Indef. flows 204	Thin broken plates	50.00	5.77	50.14	5.97
<i>p</i> -Dimethylamino- <sup>12</sup>	7	44	Froths 238	Faint yellow leaves	50.62	7.65	50.65	7.78
Unsubst. <sup>a</sup>	8	8	217	Pearly leaves	60.93	7.67	60.77	7.69
	9	38	217	Pearly leaves	60.93	7.67	60.87	7.47
	12	47	217	Pearly leaves	60.93	7.67	60.76	7.80
<i>p</i> -Methoxy- <sup>a</sup>	4	52	Indef.	Pearly leaves	57.57	7.52	57.74	7.51
	10	49	210 up	Pearly leaves	57.57	7.52	57.38	7.48
3,4-Dimethoxy- <sup>a</sup>	5	52	151	Nodules of thick irreg. prisms	55.15	7.41	55.16	7.22
<i>p</i> -Chloro-	6	50	Orange 195, dec. 215	Tiny pearly leaves	50.00	5.77	49.85	5.91

<sup>a</sup> Checked by mixed melting point determinations with authentic specimens.

TABLE IV  
BENZOYL- AND *p*-NITROBENZOYL DERIVATIVES

<i>p</i> -Nitrobenzoyl- $\beta$ -phenylethylamine	M. p., °C.	Appearance	Analysis, %			
			Calcd.		Found	
			C	H	C	H
<i>o</i> -Methoxy- $\beta$ -hydroxy-	178	Pale yellow needles	60.73	5.10	60.64	5.04
<i>o</i> -Chloro- $\beta$ -hydroxy-	194	White pearly leaves	56.15	4.09	56.40	4.21
2,3-Dimethoxy- $\beta$ -hydroxy-	178	Pale yellow crusts of hexagons	58.94	5.24	58.67	5.13
<i>o</i> -Chloro-	112	White glittering needles	59.10	4.30	59.44	4.25
<i>p</i> -Dimethylamino- (benzoyl deriv.)	130	Lemon-yellow slender needles	76.07	7.52	75.92	7.84
Unsubst.	147	White glittering needles	66.64	5.22	66.40	5.53
<i>p</i> -Methoxy- (a)	145	Faint yellow jagged needles	63.97	5.37	63.92	5.57
(b)	144	Bright orange irreg. prisms	63.97	5.37	63.66	5.36
<i>p</i> -Chloro- (benzoyl deriv.)	147	Glittering white needle prisms	69.34	5.44	69.28	5.35
<i>o</i> -Methoxy-	138	Pale yellow large needles	63.97	5.37	64.16	5.74
3,4-Dimethoxy-	147	Pale lemon glittering leaves	61.79	5.49	61.76	5.60

(12) Described as oily by Braun and Blessing, *Ber.*, **56**, 2153 (1923).

lowed to boil off and the residue heated on the water-bath for a further forty-five minutes. It was dissolved in warm benzene, shaken with dilute potassium hydroxide solution, and then washed with water. At this point the product usually crystallized out from the benzene and was filtered off, washed with water and recrystallized from alcohol, to which a little water was added. Benzoyl *p*-dimethylamino- $\beta$ -phenylethylamine and benzoyl *p*-chloro- $\beta$ -phenylethylamine were prepared by the Schotten-Baumann method, on account of difficulties encountered with the above method. The solubilities of the compounds are very similar. They are readily soluble in warm alcohol, but separate well on adding a little water to the solutions. They are soluble in warm chloroform, fairly soluble in warm benzene, and sparingly soluble in ether. The compounds are difficult to analyze and require slow burning. The  $\beta$ -hydroxy group is not nitrobenzoylated by the above procedure.

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### Summary

1. A number of mandelonitriles have been prepared in pure crystalline condition and reduced by the Adams method to  $\beta$ -hydroxy- $\beta$ -phenylethylamines or to  $\beta$ -phenylethylamines, the product being determined by the substituents in the nitrile.

2. The *p*-nitrobenzoyl or benzoyl derivatives of the amines have been prepared.

3. Several carbethoxy- or carbomethoxymandelonitriles have been similarly reduced to the  $\beta$ -phenylethylamines.

4. A number of the compounds have not been previously described.

5. Owing to its simplicity and expediency, the reduction described offers a convenient method for the preparation of certain  $\beta$ -phenylethylamines.

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