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## Reduction of Hydroxymandelonitriles. A New Synthesis of Tyramine

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In continuation of previous work<sup>1</sup> on the catalytic reduction of mandelonitriles the reduction of mandelonitriles carrying unprotected hydroxyl groups was examined. The reaction was found to proceed smoothly and to give the expected hydroxy- $\beta$ -phenylethylamine (as hydrochloride) in good yield. The method is simple and expedient and offers advantages over present methods. The hydroxymandelonitriles do not appear to have been isolated previously in a pure state, although in the case of 3,4-dihydroxymandelonitrile, mention is made of an obviously crude product.<sup>2</sup> Some of the hydroxymandelonitriles, particularly the 3,4-dihydroxy compound, have previously been reduced to the corresponding phenylethanolamine, but complete reduction to the  $\beta$ -phenylethylamine apparently is not recorded. It will be seen that the reduction of 4-hydroxymandelonitrile constitutes a new synthesis of tyramine. The reaction also permits of the preparation of  $\beta$ -phenylethylamines carrying both methoxyl and hydroxyl groups, a matter of some difficulty with most of the available methods.

### Experimental

**Hydroxymandelonitriles.**—Two methods were used to prepare the hydroxymandelonitriles. The conditions given must be closely observed. The product should be dried *in vacuo* over solid sodium hydroxide and paraffin wax.

1. The aldehyde, with sufficient absolute hydrogen cyanide to moisten it (a considerable excess over calcd.) and one per cent. of its weight of powdered catalyst, was placed in a strong bottle, the stopper wired in, and the whole kept at the temperature indicated for the time stated. In the case of the 3-hydroxy compound the reaction product was dissolved in ether and water, the ether layer washed with water, dried over calcium chloride, partly evaporated, and benzene added. The product crystallized out on standing in the refrigerator. With the 3,4-dihydroxy compound the reaction product was ground with petroleum ether and the residue extracted with ether (much brown material remained undissolved) and the extract treated with petroleum ether. A thin yellow oil separated and this, on cooling and scratching, crystallized out.

2. One mole of aldehyde (about 15 g.) was dissolved in a solution of sodium metabisulfite (2 moles) in 100 cc. of water, the solution heated to 50°, then cooled to 0°. While keeping the solution at 0° and stirring mechanically, a saturated aqueous solution of potassium cyanide (4 moles) was added dropwise over the time given. With *o*-vanillin it was necessary to work as fast as possible. The reaction mixture was extracted with ether, the ether washed with sodium metabisulfite solution, dried over calcium chloride and partly evaporated. Benzene was then added and the solution kept in the refrigerator when the product crystallized out on seeding and scratching. The nitriles are stable when pure. In general they range from readily, to very soluble in ether, alco-

(1) Buck, *THIS JOURNAL*, **55**, 2593 (1933).

(2) German Patent 193,634.

hol and water. They are sparingly soluble in petroleum ether and moderately to rather soluble in benzene and chloroform.

TABLE I  
HYDROXYMANDELONITRILES

Mandelonitrile		Method	Aldehyde used	Solvent
1	3-Hydroxy-	1	3-Hydroxybenzaldehyde	Et <sub>2</sub> O-Pet. ether
2	4-Hydroxy-	1,2	4-Hydroxybenzaldehyde	Et <sub>2</sub> O-Benzene
3	2-Hydroxy-3-methoxy-	2	<i>o</i> -Vanillin	Et <sub>2</sub> O-Pet. ether
4	3-Methoxy-4-hydroxy-	2	Vanillin	Et <sub>2</sub> O-Benzene
5	3,4-Dihydroxy-	1	Protocatechuic aldehyde	Et <sub>2</sub> O-Pet. ether

  

	Time of reaction	Catalyst	Temp., °C.	Appearance	Color
1	20 hrs.	CaO	20	Clumps of prisms	White
2	5 hrs.	CaO	50	Chalky nodules	White
			0		
3	Short as poss.		0	Felted tiny crystals or cryst. crusts	Faint cream
4	20 min.		0	Nodules of prisms	Dull white
5	2.5 hrs.	K <sub>2</sub> CO <sub>3</sub>	20	Cryst. powder	White

  

	FeCl <sub>3</sub>	Cold concd., H <sub>2</sub> SO <sub>4</sub>	Yield pure, %	M. p., °C.	Analyses, %			
					Calcd.		Found	
					C	H	C	H
1	Violet	Golden yellow soln.	66	110	64.40	4.73	64.44	5.00
2	Strong dull violet	Solid faint-green	38	98	64.40	4.73	64.35	4.94
3	Strong violet then red	Solid blackish-green	54	85	60.31	5.06	60.40	5.06
4	Dull blue	Solid red soln. faint orange	56	83	60.31	5.06	60.25	4.94
5	Intense deep green	Pale cerise soln.	63	95	58.16	4.27	58.25	4.47

TABLE II

HYDROXY- $\beta$ -PHENYLETHYLAMINE HYDROCHLORIDES

$\beta$ -Phenylethylamine hydrochloride	Color	Appearance	FeCl <sub>3</sub>
1 3-Hydroxy- <sup>a,3</sup>	Faint cream	Small glittering leaves	Faint violet
2 4-Hydroxy- <sup>b</sup> (tyramine)	White	Glittering tiny leaves	Weak dull violet
3 2-Hydroxy-3-methoxy-	Faint flesh	Glittering leaves	Deep cherry red
4 3-Methoxy-4-hydroxy- <sup>4</sup>	Grayish	Fern-like crystals	Dull blue
5 3,4-Dihydroxy- <sup>5</sup>	White	Tiny glittering leaves	Intense dark green

  

M. p., °C.	Yield, %	Analyses, %			
		Calcd.		Found	
		C	H	C	H
1 142	31 as picrate	55.31	6.98	55.20	6.62
2 > 260	48	55.31	6.98	55.25	7.09
3 175	42 as picrate	53.05	6.93	53.19	7.19
4 Orange 190 Red froth 206	77	53.05	6.93	52.71	6.79
5 Black liquid 245 Dark above 230	56	50.65	6.38	51.00	6.54

<sup>a</sup> Isolated *via* picrate. <sup>b</sup> Identical with authentic specimen.

(3) German Patent 233,551 gives m. p. 145°.

(4) Mentioned by Hamburger, *J. Pharmacol.*, **45**, 163 (1932).

(5) M. p. in literature varies. Cf. German Patent 247,906, m. p. 174-175°; Waser and Sommer, *Helv. Chim. Acta*, **6**, 60 (1923), m. p. 237° (dec.).

**$\beta$ -Phenylethylamine Hydrochlorides.**—The reduction of the mandelonitriles was carried out substantially as previously described.<sup>1</sup> The reduction was quite rapid in all cases and approximately the required amount of hydrogen was taken up (this is not always the case when hydroxyl groups are absent). 0.5 to 1.0 g. platinum oxide was used as the catalyst. The sometimes rather long incubation period was avoided by always adding some reduced catalyst from a previous preparation. Yields are recorded on the basis of the pure picrate (the best way to isolate the 3-hydroxy compound) or for the hydrochloride of the grade previously described. Recrystallization was carried out from alcohol-ether mixture until the hydrochloride was pure. The hydrochlorides are all very soluble in water and sparingly soluble in ether. Their solubility in absolute alcohol varies, but they are very to moderately soluble in 95% alcohol.

TABLE III  
DERIVATIVES

	$\beta$ -Phenylethylamine	Solvent recryst.	Appearance
1	Picrate of 3-hydroxy-	Water	Small glittering prisms
2	Di- <i>p</i> -nitrobenzoyl-3-hydroxy-	Alcohol	Minute nodules
3	4-Hydroxy-	Xylene	Glittering leaves
4	Dibenzoyl-4-hydroxy- <sup>a</sup>	Aq. alc.	Felted glittering needles
5	Picrate of 2-hydroxy-3-methoxy-	Water	Long glittering needles
6	Dibenzoyl-3-methoxy-4-hydroxy-	Aq. alc.	Tiny glittering needles
7	Tribenzoyl-3,4-dihydroxy-	Aq. alc.	Slender needles

Color	M. p., °C.	Analyses, %			
		Calcd.		Found	
		C	H	C	H
1 Deep yellow	170	45.89	3.85	46.10	4.23
2 White	157	60.67	3.94	60.75	3.80
3 Faint biscuit	157	70.02	8.09	70.03	8.12
4 White	172	76.48	5.55	76.37	5.51
5 Deep golden	170	45.44	4.07	45.32	4.52
6 White	129	73.57	5.64	73.43	5.42
7 Pale gray	140	74.81	4.98	74.55	5.51

<sup>a</sup> Ehrlich and Lange, *Biochem. Z.*, **63**, 167 (1914).

**Derivatives.**—For analytical check mainly, one or more derivatives were made of each amine. Those given are probably the easiest to obtain. The picrates were obtained by the action of the theoretical amount of sodium picrate, in aqueous solution, on an aqueous solution of the hydrochloride. The benzoyl derivatives were made by the Schotten-Baumann method, and the *p*-nitrobenzoyl derivative by the method given in the previous paper. 4-Hydroxyphenylethylamine (base) was isolated by the usual method and was identical with tyramine.

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### Summary

Five hydroxy mandelonitriles have been prepared in a pure state and reduced catalytically to the corresponding hydroxy- $\beta$ -phenylethylamines. A new method for the synthesis of tyramine is described.

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