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Catalytic Reduction of Mandelonitriles

By Johannes S. Buck

In an attempt to simplify the preparation of β -phenylethylamines, the catalytic reduction of mandelonitriles was investigated. Some previous work in this direction has been cited by Hartung.¹ Little seems to have been done at moderate pressures and at room temperature. Kindler² reports that the reaction fails, and³ that acylated nitriles reduce badly, giving poor yields of the β -phenylethylamines. Paal and Gerum,⁴ in earlier work, reduced mandelonitrile, using palladium, to benzyl alcohol, benzylamine, dibenzylamine and ammonia. Hartung¹ gave details for the reduction of mandelonitrile to β -phenylethylamine and noted the non-production of β -hydroxy- β -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 β -phenylethylamine or β -hydroxy- β -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 β -phenylethylamines. Of the nitriles examined, those with ortho substituents gave the β -hydroxy- β -phenylethylamine, the others giving the β -phenylethylamine. No meta-substituted nitriles were prepared in a state of sufficient purity for reduction. Kindler⁵ 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 β -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).

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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 Parry⁶ 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.⁷ (3) The bisulfite compound of the aldehyde was treated with potassium cyanide solution, in a manner similar to that of Kostanecki and Lampe.⁸

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 $25-30^{\circ}$. The resultant oil solidified on standing in the refrigerator and the solid was then ground with petroleum ether (b. p. $30-60^{\circ}$), filtered off, washed with petroleum ether

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MANDELONITRILES

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

| | | I ADLE I | (Concinueu) |) | | |
|----------|------------------|----------|-------------|---------|---------|------|
| | Color, cold | | Cal | | vsis, % | und |
| No. | H2SO4 | M. p. | c | н. Н | c | н |
| 1 | Solid blue-green | 73 | 66.23 | 5.56 | 66.37 | 5.40 |
| 2 | Strong magenta | 47 | 57.29 | 3.57 | 57.13 | 3.87 |
| 3 | Deep wine-red | 79 | 62.15 | 5.74 | 62.12 | 6.13 |
| 4 | Solid blue-green | 67 | 66.23 | 5.56 | 66.05 | 5.52 |
| ,5 | Pale orange-red | 103 | 62.15 | 5.74 | 62.33 | 5.98 |
| 6 | Intense violet | 43 | 57.29 | 3.57 | 57.27 | 3.70 |
| | | | | | | |

| TABLE I | (Concluded) |
|---------|-------------|

^a Mentioned but not described by Pictet and Gams⁹ and Kindler.¹⁰ In addition to the above, p-dimethylaminomandelonitrile No. 7 and mandelonitrile No. 8 were both prepared by Method 2.

and recrystallized from ether-petroleum ether mixture. So obtained, the nitriles are mostly fairly stable and reduce readily. As a rule, the nitriles are very soluble in the usual solvents and very or moderately soluble in ether. In petroleum ether, they are rather slightly soluble.

Reduction of Carbethoxy- and Carbomethoxymandelonitriles.—Carbethoxymandelonitrile was prepared by the method of Francis and Davis¹¹ and the other three compounds were obtained by practically the same procedure. The reduction was carried out in a manner similar to that of the mandelonitriles, and it proceeded in much the same way as with the non-acylated compounds. The products were isolated and identified in the manner already described. The following results were obtained carbomethoxymandelonitrile gave β -phenylethylamine hydrochloride in 38% yield; carbethoxymandelonitrile gave β -phenylethylamine hydrochloride in 47% yield; o-chlorocarbethoxymandelonitrile gave ρ -chloro- β -phenylethylamine hydrochloride in 94% yield, and p-methoxycarbethoxymandelonitrile gave homoanisylamine hydrochlorochloride in 49% yield.

| CARBOMETHO | XY AND CARBET | HOXYMANDELONIT | RILES |
|-----------------------------|---------------|----------------|-------|
| Compound, mandelonitrile | Color | B. p., °C. | ä |
| methowy | Colorless | 126 (3 mm) | 1 1 |

TABLE II

| No. | -mandelor | itrile | Color | B. p., °C. | <i>d</i> ₄ | n _D |
|----------|-----------------------------|-----------|-------------------|--------------|-----------------------|----------------|
| 9 | Carbomethor | кy | Colorless | 136 (3 mm.) | 1.1735 | 1.5000 |
| 10 | p-Methoxyca | rbethoxy | Faint yellow | 170 (2.1 mm. |) 1.1683 | 1.5063 |
| 11 | o-Chlorocarb | ethoxy | Colorless | 145 (1.4 mm. |) 1.2444 | 1.5115 |
| | | | | Ana | lysis, %—— | |
| | $M_{\rm D}$ c | alcd. | | Calcd. | | ound |
| | | | | | | |
| No. | | Eisenlohr | $M_{\rm D}$ found | с н | c î | Н |
| No. 9 | Brühl | | 2 | | | |
| | Brühl [~] 48.30 | Eisenlohr | 47.87 | С Н | С | н |

Carbethoxymandelonitrile¹¹ was also used (No. 12). The odors are very faint (nitrile). Except for the *p*-methoxy compound, the nitriles are practically colorless. They are rather viscous liquids, insoluble in water but miscible with the usual solvents. They are sparingly soluble in petroleum ether, and are quite stable.

Benzoyl- and p-Nitrobenzoyl Derivatives.—The method of preparation was usually to reflux the hydrochloride of the amine with twice its weight of p-nitrobenzoyl chloride and twenty times its weight of benzene for thirty minutes. The benzene was then al-

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⁽⁹⁾ Pictet and Gams, Ber., 42, 2943 (1909).

⁽¹⁰⁾ Kindler and Peschke, Arch. Pharm., 269, 581 (1931).

⁽¹¹⁾ Francis and Davis, J. Chem. Soc., 95, 1409 (1909).

| | | | | | | Апа. | Iysis | |
|--|----------|-----------|----------------------|--------------------------------|---------|------|-------|------|
| | Nitrile | Yield. | | | Calcd | | Fou | ınd |
| β -Phenylethylamine | reduced | % | M. p., °C. | Appearance | с | н | С | н |
| o-Methoxy-β-hydroxy- | 1 | 59 | 184 | Tiny thin plates | 53.05 (| 5.93 | 53.22 | 6.97 |
| o-Chloro-β-hydroxy- | 2 | 41 | 197 | Crusts of broken prisms | 46.15 | 5.33 | 46.32 | 5.61 |
| 2,3-Dimethoxy-β-hydroxy- | 3 | 23.5 | 134 | Tiny jagged plates | 51.37 6 | 5.90 | 51.52 | 6.82 |
| o-Chloro- | 11 | 94 | Indef. flows 204 | Thin broken plates | 50.00 | 5.77 | 50.14 | 5.97 |
| <i>p</i> -Dimethylamino- ¹² | 7 | 44 | Froths 238 | Faint yellow leaves | | 7.65 | 50.65 | 7.78 |
| Unsubst. ^a | 8 | 8 | 217 | Pearly leaves | | 7.67 | 60.77 | 7.69 |
| | 9 | 38 | 217 | Pearly leaves | 60.93 7 | 7.67 | 60.87 | 7.47 |
| | 12 | 47 | 217 | Pearly leaves | 60.93 7 | 7.67 | 60.76 | 7.80 |
| p-Methoxy- ^a | 4 | 52 | Indef. | Pearly leaves | | 7.52 | 57.74 | 7.51 |
| - | 10 | 49 | 210 up | Pearly leaves | 57.57 7 | 7.52 | | 7.48 |
| 3,4-Dimethoxy- ^a | 5 | 52 | 151 | Nodules of thick irreg. prisms | | 7.41 | | 7.22 |
| p-Chloro- | 6 | 50 | Orange 195, dec. 215 | Tiny pearly leaves | 50.00 8 | 5.77 | 49.85 | 5.91 |
| | | | | | | | | |

TABLE III

Hydrochlorides of β -Phenylethylamines and β -Hydroxy- β -Phenylethylamines

^a Checked by mixed melting point determinations with authentic specimens.

TABLE IV BENZOVL- AND p-NITROBENZOVL DERIVATIVES

| p-Nitrobenzoyl- | | | Cal | cd. | | und |
|-----------------------------------|------------|--------------------------------|-------|------|-------|------|
| β -phenylethylamine | M. p., °C. | Appearance | с | н | С | н |
| o-Methoxy-β-hydroxy- | 178 | Pale yellow needles | 60.73 | 5.10 | 60.64 | 5.04 |
| o-Chloro-β-hydroxy- | 194 | White pearly leaves | 56.15 | 4.09 | 56.40 | 4.21 |
| 2,3-Dimethoxy-β-hydroxy- | 178 | Pale yellow crusts of hexagons | 58.94 | 5.24 | 58.67 | 5.13 |
| o-Chloro- | 112 | White glittering needles | 59.10 | 4.30 | 59.44 | 4.25 |
| p-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 |
| p-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 |
| p-Chloro- (benzoyl deriv.) | 147 | Glittering white needle prisms | 69.34 | 5.44 | 69.28 | 5.35 |
| o-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).

-Analysis, %

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- β -phenylethylamine and benzoyl p-chloro- β -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 β -hydroxy group is not nitrobenzoylated by the above procedure.

The writer is indebted to Mr. W. S. Ide for the large number of microanalyses done in the course of the foregoing work.

Summary

1. A number of mandelonitriles have been prepared in pure crystalline. condition and reduced by the Adams method to β -hydroxy- β -phenylethylamines or to β -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 β -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 β -phenylethylamines.

TUCKAHOE, NEW YORK

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