

# REDUCTION OF AROMATIC CARBONYL COMPOUNDS WITH NICKEL/ALUMINIUM ALLOY

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The reduction of aromatic carbonyl compounds by means of nickel/aluminium alloy in alkaline solutions and suspensions has been examined and results were obtained that were different from certain of those reported earlier. Improvements in the technique are described.

## Introduction

The reduction of carbonyl compounds with nickel/aluminium alloy and aqueous alkali-metal hydroxides has been described by a number of authors,<sup>1-4</sup> although the technique and the composition of the reaction products have apparently not been fully investigated. In the present work, chromatographic methods (g.l.c. and t.l.c.) were used rather than a spectroscopic method (infra-red)<sup>5</sup> for identification of products. Papa *et al.*<sup>1</sup> reported the formation of hydrocarbons ( $\text{ArCH}_2\text{R}$ ) which were identified only by b.p. or m.p., from conjugated carbonyl compounds ( $\text{ArCOR}$ ;  $\text{R} = \text{H}$  or alkyl), and carbinols ( $\text{Ar}(\text{CH}_2)_n\text{CH}(\text{OH})\text{R}$ ) (I) from non-conjugated compounds ( $\text{Ar}(\text{CH}_2)_n\text{COR}$ ;  $\text{R} = \text{H}$  or alkyl,  $n > 1$ ). A repetition of this method and reduction under considerably more drastic conditions failed to yield the described results. Extensive investigation has now shown that both classes of ketones yield carbinols (I) and  $\text{ArCH}(\text{OH})\text{R}$  with negligible hydrogenolysis. Unfortunately, the results described<sup>1</sup> have been quoted in other sources.<sup>6-7</sup> Aromatic aldehydes are more prone to yield the corresponding hydrocarbon accompanied by the carbinol. Considerable improvement in the reaction techniques, resulting in economy in alloy consumption, smoother reaction and easier manipulation, has been achieved by addition of the alkaline solution to the remaining ingredients, which is the reverse of the usual procedure, and by increase in the reaction time. The efficiency of this procedure may possibly be associated with the fact that Raney nickel contains 50-100 ml of hydrogen/g of nickel<sup>8</sup> and its activity is apparently dependent on the sequence of operations used in its preparation.<sup>9</sup>

## Experimental

Nickel/aluminium alloy (50:50) was used. Previous workers have added an excess of the alloy (8-10 M) to the compound in solution with excess aqueous alkali (6 M), usually in an open apparatus. It was clear from a considerable number of experiments with acetophenone that reversal of this procedure resulted in easier manipulation, economy of reagents and improved yields.

All complete reaction products were examined, if volatile, by g.l.c. on different stationary phases including polypropylene sebacate and Apiezon L (10% on celite). Products after purification were identified by the use of reference compounds and independent methods of preparation. All complete reaction mixtures were analysed for the percentages of carbonyl compounds and carbinols present.

Non-volatile reaction mixtures and compounds were examined by t.l.c. on silica gel G (Merck).

Reductions under three different sets of conditions are described in the following experimental work: in aqueous alkaline solution, in the presence of organic bases, and in neutral solution. Retention times (r.t.) are given in minutes.

## Reductions in alkaline solution

### $\alpha$ -Phenylethyl alcohol

An attempt was made to repeat the reduction described by Papa *et al.*<sup>1</sup>

Acetophenone (10 g; 0.083 mole), sodium hydroxide (30 g; 0.75 mole) and water (300 ml) were stirred at 90° and nickel/aluminium alloy (30 g) was added in small portions. The mixture was then stirred and heated at 90° for 1 h, cooled, filtered, and the product recovered by ether extraction. Evaporation gave a residue (5 g) that consisted of  $\alpha$ -phenylethyl alcohol containing acetophenone (12.6%).

Under more drastic conditions at 100° with acetophenone (0.1 mole), potassium hydroxide (0.24 mole), water (90 ml) and nickel/aluminium alloy (30 g), the product contained  $\alpha$ -phenylethyl alcohol (81%),  $\alpha$ -cyclohexylethyl alcohol (5%), cyclohexyl methyl ketone (3.8%) and acetophenone (5.3%) together with a little ethylbenzene.

*Preparative-scale g.l.c. separation of acetophenone reduction products.* Separation of the components of the reduction products obtained under the above conditions was carried out using a preparative column (22 ft  $\times$  1 in) of 30% polypropylene sebacate (30%) on celite at 140°, with nitrogen flow 1400 ml/min and argon flow 140 ml/min (through the ionisation detector only, by means of a by-pass).

The order of emergence was ethylbenzene (r.t. 3.1), cyclohexyl methyl ketone (I) (r.t. 13),  $\alpha$ -cyclohexylethyl alcohol (II) (r.t. 24), acetophenone (r.t. 34) and  $\alpha$ -phenylethyl alcohol (r.t. 62). No ethylcyclohexane was detected. The presence of ethylbenzene was confirmed by identifying the infra-red spectrum with an independently prepared sample and comparison with the Sadtler spectrum. Cyclohexyl methyl ketone was synthesised by rearrangement of cyclohexyl ethynyl carbinol in benzene containing phosphorus pentoxide to 1-acetylcyclohexene, followed by selective hydrogenation. It was identical with (I) in all respects. (II) was identical with product of hydrogenation of  $\alpha$ -phenylethyl alcohol over the Adams' catalyst. Found: C, 76.2; H, 12.6%. Calc. for  $\text{C}_8\text{H}_{16}\text{O}$ : C, 76.1; H, 12.6%.

*Modified reduction procedure.* It was found possible to avoid the small amounts of minor products obtained with the above procedure, and a considerable number of preparatory experiments showed the following conditions to be the best.

Acetophenone (206 g), nickel/aluminium alloy (68 g) and water (385 ml) were mechanically stirred at the ambient temperature in a glass vessel, equipped with a vacuum-sealed glass stirrer gland, and surrounded by a cooling bath containing a circulatory pump. During the addition (1 h, from a pressure-equalised funnel) of a solution of sodium hydroxide (87 g) in water (80 ml), the internal temperature increased to 30° and the pressure by a few mm of mercury. After a further 1½ h, the external temperature was raised to 46° by means of a Circotherm unit and the reaction mixture stirred overnight.

The flask contents, consisting of an upper liquid layer and a lower layer of heavy nickel catalyst with a suspension of aluminium salts, were removed by vacuum through a filter (solid was kept moistened in the final stages since it is sometimes pyrophoric). The solid was washed with water, then with carbon tetrachloride or benzene, and finally with water. After digestion with sodium hydroxide solution to remove aluminium salts, the recovered nickel catalyst could be stored in aqueous or methanolic suspension for use as a hydrogenation catalyst. The organic material (199 g) obtained after recovery of the solvent contained  $\alpha$ -phenylethyl alcohol (92.3%; 87% yield), the remainder consisting of acetophenone and a negligible amount of ethylbenzene (g.l.c.). T.l.c. likewise indicated that only two substances were present. By fractional distillation under high reflux,  $\alpha$ -phenylethyl alcohol, b.p. 205°/760 mm, was separated from a fore-run of acetophenone, b.p. 202°/760 mm. Found: C, 78.5; H, 8.2%. Calc. for  $C_8H_{10}O$ ; C, 78.5; H, 8.2%. 3,5-Dinitrobenzoate m.p. and mixed m.p.: 94°.

The reduction was successful on a 1200-g scale provided that completely adequate cooling and emergency quenching precautions were available (essential for safe operation of this exothermic reaction). Excellent yields were obtained in all experiments carried out between ambient temperature and 100°.

#### $\alpha$ -(*p*-Methoxyphenyl)ethyl alcohol

A stirred solution of *p*-methoxyacetophenone (15 g) in ethanol (115 ml), containing potassium hydroxide (13.5 g) and water (35 ml), was cooled to -10°. Nickel/aluminium alloy (30 g) was added in small portions while the temperature rose to 20°. The filtered reaction mixture was concentrated after 3 h and the extracted and washed product (12 g) was distilled, b.p. 128–131°/10 mm, to give unchanged *p*-methoxyacetophenone, 38.2%, and  $\alpha$ -(*p*-methoxyphenyl)ethyl alcohol, 57.2% [g.l.c. and analysis for  $>C=O$  and  $>CH(OH)$ ]. The mixture could be separated by fractionation or preparative g.l.c. on a 22 ft  $\times$  1 in column of 10% Apiezon L on celite at 120°.

In a preparation carried out at a higher temperature, 20% of a new component was noted. The six materials present were separated by preparative g.l.c., and were identified as *p*-methoxyethylbenzene (r.t. 7.1) identical with the product of Wolff-Kishner reduction of the ketone, 4-methoxycyclohexyl methyl ketone (III) (r.t. 13.4),  $\alpha$ -(4-methoxycyclohexyl)ethyl alcohol (IV) (r.t. 20.0) (insufficient of (III) and (IV) were available for complete identification), ethyl ether of  $\alpha$ -(*p*-methoxyphenyl)ethyl alcohol (r.t. 26.8) (from infra-red and mass spectra), *p*-methoxyacetophenone (V) (r.t. 31.9), and  $\alpha$ -(*p*-methoxyphenyl)ethyl alcohol (VI) (r.t. 40.9). Found: C, 70.6; H, 8.0%. Calc. for  $C_9H_{12}O_2$ : C, 71.0; H, 8.0%. The infra-red spectra of (V) and (VI) were in agreement with expectation.

#### Other aromatic carbonyl compounds

Under identical conditions at 40–50°, in experiments where the alloy (30 g) was added to the remaining reactants (0.1 mole of ketone), conversions to  $\alpha$ -phenylethyl alcohol,  $\alpha$ -phenylpropyl alcohol, and  $\alpha$ -phenylbutyl alcohol were 91%, 81% and 42%, respectively. In the last case, reversal of the order of addition gave a considerable improvement in yield and economy in alloy consumption.  $\beta$ -Benzoylpropionic acid gave  $\gamma$ -phenyl- $\gamma$ -butyrolactone (identified by g.l.c.). A few aromatic aldehydes were reduced. Thus benzaldehyde gave a small yield of benzyl alcohol accompanied by toluene. Similarly, *p*-dimethylaminobenzaldehyde gave *p*-dimethyl-

aminobenzyl alcohol and *p*-dimethylaminotoluene (g.l.c. analysis). As described later, yields of carbinols were improved with the aid of aqueous organic bases.

Table I summarises some of the results obtained. Experiments (O), in which an excess of alloy was used, were carried out before the reversed procedure (R) was adopted and there was no opportunity to repeat them.

#### ( $\pm$ )- $\alpha$ -Phenyl- $\beta$ -methylaminopropyl alcohol (ephedrine)

( $\pm$ )- $\alpha$ -Methylaminopropiophenone ('ephedrone') was prepared from  $\alpha$ -bromopropiophenone by interaction with methylamine and had an  $R_F$  value (chloroform/diethylamine, 9:1, Dragendorff's reagent) identical to that of the product of oxidation of ephedrine with sodium *t*-butoxide in dry benzene containing benzophenone.<sup>10</sup> Reduction in hot ethanolic solution by the reversed procedure gave a low yield of ephedrine, accompanied by much unchanged ephedrone but no hydrogenolysis product. T.l.c. examination (chloroform/diethylamine, 9:1, iodoplatinate reagent) showed that a negligible proportion of pseudo-ephedrine ( $R_F$  0.40) had been formed (ephedrine, ( $\pm$ ) or (-),  $R_F$  0.33). Randerath<sup>11</sup> has reported that ephedrine gave rise to elongated spots but the  $R_F$  value was not recorded. In the present work, distinct spots were observed under conditions where brucine gave the described value ( $R_F$  0.63).

#### Meso-Hydrobenzoin

*Meso*-Hydrobenzoin was formed at refluxing temperature and benzoin at lower temperatures. The following conditions were found to be the best from a number of preparations. 12% sodium hydroxide (15 ml) was gradually added to benzoin (2.0 g) in boiling ethanol (30 ml) containing nickel/aluminium alloy (0.6 g). The mixture became yellow and was filtered after being refluxed for 2 h. The precipitate collected from the acidified filtrate was extracted (Soxhlet) with hot water to separate *meso*-hydrobenzoin (0.6 g) from benzoin (0.4 g). Evaporation gave a further yield of the former, and the combined material (containing some desoxybenzoin and benzoin) was extracted with light petroleum (60–80°) to leave *meso*-hydrobenzoin which crystallised from water as glistening plates, m.p. 132–133° (identical with the product obtained by reduction of benzoin with sodium borohydride and catalytic reduction with Raney nickel at 1 atm). Found: C, 78.2; H, 6.56%. Calc. for  $C_{14}H_{14}O_2$ : C, 78.5; H, 6.58%. The presence of traces of dibenzyl (odour), desoxybenzoin and benzoic acid was confirmed by t.l.c.

Benzil (2.0 g) in ethanol (40 ml) containing nickel/aluminium alloy (2.0 g) was warmed during the gradual addition of 12% aqueous sodium hydroxide (15 ml). The dark mixture was filtered after 2 h and the brown solid obtained on dilution with water was crystallised (charcoal) from ethanol to give 0.8 g of product, m.p. 130°. Further crystallisation yielded pure benzoin. Some desoxybenzoin was identified by t.l.c. Found: C, 79.6; H, 5.8%. Calc. for  $C_{14}H_{12}O_2$ : C, 79.2; H, 5.7%.

Schwenk *et al.*<sup>12</sup> obtained hydroanisoin from anisoin but gave no details. All reaction mixtures and products were examined on silica gel G impregnated with 10% boric acid, in the absence of which the separation of *meso*- and ( $\pm$ )-hydrobenzoin was smaller (solvent: diethyl ether/light petroleum, 40–60°, 50/50 by volume). ( $\pm$ )-Hydrobenzoin (m.p. 120°,  $R_F$  0.33), *meso*-hydrobenzoin (m.p. 132°,  $R_F$  0.27), benzoin ( $R_F$  0.48), desoxybenzoin (m.p. 58°,  $R_F$  0.70), dibenzyl ( $R_F$  0.85) and benzil ( $R_F$  0.63) reference compounds were prepared by standard procedures.<sup>7</sup>

TABLE I

Ketone, g (moles)	Method	Base, (mole)	Temp., °C	Alloy, g	Solvent, ml	Conversion, %		Total product, g	Yield of carbinol, % (on ketone taken)	Yield, % (on ketone used)*
						Carbinol	Ketone			
Butyrophenone 75 (0.506)	R	NaOH (0.37) in 50 ml H <sub>2</sub> O	40-50	17	W, 400	76.3	23.7	70	70.3	90.2 ( $\alpha$ -phenylbutyl alcohol)
$\beta$ -Dimethylamino- propiofenone HCl 10 (0.47)	O	NaOH (0.3)	60-70	—	W, 30	100	—	2.6	—	$\alpha$ -phenylpropyl alcohol
Benzophenone 18.2 (0.1)	O	KOH (0.24)	40-50	50	E/W, 50/50	76.7	19.5	16.5	68.8	83.6 (benzylhydrol)
2-Acetylnaphthalene 17.0 (0.123)	O	KOH (0.24)	90	30	W/EG, 25/75	60.5	4.2	15.8	55.6	65.4 ( $\alpha$ -(2-naphthyl)ethyl alcohol)
<i>p</i> -Isopropylacetophenone 16.2 (0.1)	R	KOH (0.24) in 40 ml	40-50	30	W, 50	75.6	21.9	13	59.9	72.7 ( $\alpha$ -( <i>p</i> -isopropylphenyl)ethyl alcohol)
<i>p</i> -Chloroacetophenone 7.75 (0.5)	R	KOH (0.12) in 20 ml	20-30	15	W, 40	96.9	3.0	4.0	63.5	64.6 ( $\alpha$ -phenylethyl alcohol)
<i>p</i> -Nitroacetophenone 8.25 (0.1)	O	KOH (0.24)	20	15	E/W, 50/50	100	—	—	—	( $\alpha$ - <i>p</i> -aminophenylethyl alcohol, m. p. 98°)

W = water, E = industrial methylated spirit, EG = ethylene glycol O = ordinary procedure, R = reversed procedure \* allowing for recovery of unused ketone

### 9,10-Anthraquinone

Commercial 9,10-anthraquinone was purified by crystallisation from chloroform/benzene to give needles, m.p. 282–284°, having correct elementary analysis. The following were found to be the best conditions from a number of trials. Anthraquinone (5.0 g) in diethylene glycol (65 ml) containing nickel/aluminium alloy (5 g) was treated for 2 h at 150° with 12% aqueous sodium hydroxide (100 ml) and then maintained at 170° for 2 h. The partly cooled mixture was filtered from some unchanged anthraquinone and the dark filtrate acidified to give a pale orange product (m.p. 140–165°).

A portion of the crude reduction products (1.615 g) was extracted with 10% aqueous sodium hydroxide (50 ml). The filtrate was acidified and crystallised to give pale yellow prisms of *trans*-9,10-dihydroxy-9,10-dihydroanthracene (0.262 g), m.p. 140–142° (from methanol) (Boyland & Manson<sup>13</sup> give m.p. 140–142°). The alkali-insoluble material contained anthraquinone. Found: C, 80.1; H, 5.7%. Calc. for C<sub>14</sub>H<sub>12</sub>O<sub>2</sub>: C, 79.5; H, 5.7%. The *cis* isomer, m.p. 160–161°, was not present in more than trace amounts (t.l.c.).

Another portion of the crude products (0.219 g) was first separated into a methanol-soluble fraction (0.191 g) and an insoluble fraction (0.028 g). The former was separated by preparative t.l.c. which indicated the presence of at least five components. From eleven portions of silica gel G collected, the fourth (0.108 g) represented the major band. After methanolic crystallisation this gave the *trans* product, m.p. 140–142° (visualisation on analytical scale thin-layer plates by means of iodine or concentrated sulphuric acid). The following compounds were present in addition to unchanged anthraquinone: anthrone (*R<sub>F</sub>* 0.54), oxanthrol (resulting from alkali treatment of anthrone), dihydroanthrone (*R<sub>F</sub>* 0.29), traces of 9,10-dihydroanthracene (*R<sub>F</sub>* 0.68), *trans*-9,10-dihydroxyanthracene (*R<sub>F</sub>* 0.22) and traces of the *cis* isomer (*R<sub>F</sub>* 0.16). The first four compounds were all prepared by standard procedures,<sup>7</sup> and t.l.c. clearly indicated that the classical reduction procedures all give mixtures and the more 'selective' reagents<sup>13,14</sup> are also far from specific. Solutions of the reaction mixture from the alloy reduction were fluorescent and it was clear that anthraquinol was certainly produced but was rapidly oxidised in the alkaline solution to anthraquinone during the working-up stage.

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### Reductions in aqueous solutions of organic bases

The base (usually 20 g) was added to acetophenone (0.1 mole) and nickel/aluminium alloy (30 g) suspended in water (90 ml), and the reaction was carried out over 4 h at 50–60°. There appeared to be little advantage in heating reaction mixtures above this temperature. The sole product in all cases was  $\alpha$ -phenylethyl alcohol and the following amounts of residual ketone were obtained with: quinoline (0.155 mole), 1.2%; morpholine (0.23 mole), 2.1%; (0.023 mole), 2.0%; triethanolamine (0.15 mole), 3.28%. Benzyltrimethylammonium hydroxide (0.084 mole, 21.8% ketone unreacted), triethylamine (0.2 mole) and ammonia (1.27 mole, as 36% aqueous ammonia) were less effective. Ammonia gave  $\alpha$ -phenylethylamine by reductive amination as well as  $\alpha$ -phenylethyl alcohol (g.l.c.). Benzaldehyde (0.1 mole) reacted with nickel/aluminium alloy in aqueous triethylamine to give benzylalcohol and some unchanged benzaldehyde, but no toluene.

### Reductions in neutral solution

Reduction in neutral solution was a vigorous reaction and the products in the case of acetophenone depended on the temperature. Insufficient work has been carried out for generalisations to be made. Acetophenone (0.1 mole) in water (90 ml) containing nickel/aluminium alloy (30 g) reacted at 50–60° to give a product (6.75 g) that contained  $\alpha$ -phenylethyl alcohol (66.3%), acetophenone (2.3%) and ethylbenzene (31%). Reduction occurred rapidly at 90° to give ethylbenzene containing cyclohexyl methyl ketone (8.4%).

### Reduction in the presence of palladised charcoal

Acetophenone (0.1 mole), potassium hydroxide (13.5 g), water (90 ml) and 10% palladised charcoal (4.0 g) were treated with aluminium powder (15 g) at 40–50° for 3 h. The product (10 g) contained only acetophenone and  $\alpha$ -phenylethyl alcohol (conversion 58%). Similar results were obtained with Adams' catalyst.

### Results and discussion

Under the modified conditions (at ambient temp., 50° or 100°), acetophenone gave an excellent yield of  $\alpha$ -phenylethyl

alcohol and *p*-methoxyacetophenone gave  $\alpha$ -(*p*-methoxyphenyl)ethyl alcohol, whereas Papa *et al.*<sup>1,12</sup> isolated only ethylbenzene in both cases. Homologous and nuclear-substituted ketones yielded the corresponding carbinols except in the case of the *p*-chloro- and *p*-nitro-phenyl compounds where simultaneous dehalogenation and reduction to the *p*-amino compounds occurred. When the method was applied to the reduction of ( $\pm$ )- $\alpha$ -methylaminopropiophenone ('ephedrone'), which is normally carried out catalytically with a palladium or platinum catalyst, a low yield of ( $\pm$ )-ephedrine (with little pseudo-ephedrine) was obtained, with a considerable proportion of recoverable ketone and none of the corresponding hydrocarbon. Polycyclic ketones generally required higher temperatures for efficient reduction and ethylene glycol was the most useful solvent. Benzoin yielded *meso*-hydrobenzoin rather than the ( $\pm$ ) compound, both of which could be differentiated by t.l.c. with boric acid-impregnated silica gel G.<sup>15</sup> Benzil gave benzoin under mild reduction conditions with almost complete absence of benzilic acid.

9,10-Anthraquinone yielded a number of products, the chief of which was *trans*-9,10-dihydroxy-9,10-dihydroanthracene with traces of the *cis* isomer.<sup>16</sup> Minor products were anthrone, dihydroanthrone and some anthraquinol which was readily oxidised to anthraquinone. The alloy reduction procedure was found to be a more convenient method for the preparation of the *trans* compound than the lithium aluminium hydride and aluminium isopropoxide reductions previously described.<sup>13,14</sup> During the search for milder conditions, particularly for use with aromatic aldehydes, the influence of basicity of the reaction medium was examined. Experiments with a series of aqueous organic bases of decreasing  $K_b$  values indicated that reduction was still occurring together with consumption of aluminium usually associated only with inorganic bases. The use of the alloy in this manner and also in hot, neutral aqueous solution appears to be novel. Under the former conditions, reduction of acetophenone to the carbinol proceeded at little more than ambient temperature, while in the latter case, interaction of the alloy with water did not occur until the temperature of the

reaction mixture had reached approximately 70°<sup>17</sup> and reduction was more extensive. Thus, acetophenone in hot, neutral solution gave ethylbenzene. The rate of reduction was accelerated by organic as opposed to inorganic bases, although under basic conditions the reduction was generally confined to the carbinol stage. Adkins & Billica have reported<sup>18</sup> increased rates of hydrogenation with Raney nickel in the presence of tertiary bases.

It is clear from the present work that the alloy reduction does not resemble the Clemmensen reduction as supposed by Papa *et al.*<sup>1</sup> but rather Raney nickel hydrogenation. Numerous such hydrogenations have justified this comparison. The alloy reduction is essentially a hydrogenation procedure carried out under chemical reduction conditions, with substantially no free hydrogen in the modified procedure described in this work.

The association of alloyed metals results in efficient reduction which is not observed with the powdered, admixed metals. The catalytic character of the reduction with the alloy is emphasised by the occurrence of comparable results with palladised charcoal/aluminium mixtures in alkaline solution.

The application of the 'reversed' procedure for the reduction of other functional groups is being investigated.

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