

## A New One Step Indole Synthesis

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A simple conversion of 2-(*o*-nitrophenyl)ethanol to indole in the gas phase over a copper catalyst was presented. The probable way of formation of indole was discussed. The most probable intermediates were thought to be 2-(*o*-aminophenyl)ethanol (2) and 2,3-dihydroindole (3). Part of the reaction might proceed *via o*-aminophenylacetaldehyde (9).

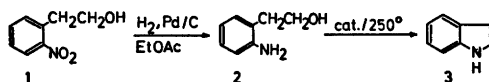
Most of the methods for the synthesis of indole (3) result primarily in substituted indoles.<sup>1</sup> Lately an interest in simple, direct methods for the synthesis of indole itself has been noted. Thus, a number of groups have been working on the high temperature conversion of *o*-aminoethylbenzene to indole,<sup>2,3</sup> and lately Suvorov, Avramenko, Shilkova and Zamyshlyeva<sup>4</sup> were able to convert acetaldehyde phenylhydrazone to indole in 60 % yield by catalytic reaction in the vapour phase.

Some time ago, we reported the addition of mononitrotoluenes to aldehydes.<sup>5</sup> The products from the reaction between some *o*-nitrotoluenes and various aldehydes have been used to synthesize both substituted and unsubstituted indoles and 2,3-dihydroindoles.<sup>6</sup> 2-(*o*-Nitrophenyl)ethanol (1), readily available from *o*-nitrotoluene and formaldehyde, gave indole (3) or 2,3-dihydroindole (3) by that reaction sequence. Although the yields in each step were high, the number of steps necessary made it desirable to find a more direct synthesis of indole and 2,3-dihydroindole.

By running reactions in gas phase it is sometimes possible to carry out several consecutive synthetic steps without isolation and purifica-

tion of the intermediate products. The possibility of a gas phase conversion of 2-(*o*-nitrophenyl)ethanol to indole was therefore investigated.

Several years ago, Ufer and Breuers<sup>7</sup> described the formation of indole from 2-(*o*-aminophenyl)ethanol (2) by gas phase reaction over a copper catalyst. As 2-(*o*-aminophenyl)ethanol was readily available from the nitro analogue this method was tried:



No yield was stated in the German patent, and our reproduction indicated the catalyst to have a rather short working life (less than 10 min). Ufer *et al.*<sup>7</sup> had prepared the catalyst by shaking bauxite with dry copper carbonate, followed by reduction. In that way, copper would be present only on the outer surface of the catalyst particles, and not in the internal pore structure.

A far superior catalyst was made by soaking silica gel in a solution of copper nitrate, drying and reducing with hydrogen. This is a well known method for the preparation of metal catalysts on carriers, and in this way even the inner pores of the carrier will contain metal catalyst. By using this type of preparation, catalysts with a working life of several hundred hours were obtained. The yield (95 %) and purity (96 %) of the indole produced was high. We had thus obtained a two step synthesis of indole from 2-(*o*-nitrophenyl)ethanol: reduction of the nitro group to an amino group in the liquid phase, followed by the vapour phase synthesis of indole.

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However, the vapour phase reduction of aromatic nitro compounds to the corresponding amines is a well known process.<sup>8</sup> If therefore 2-(*o*-nitrophenyl)ethanol could be reduced in the vapour phase without decomposition, the reaction would proceed directly to indole, and a one step synthesis of indole from 2-(*o*-nitrophenyl)ethanol would be obtained.

When 2-(*o*-nitrophenyl)ethanol was passed over the copper catalysts used for the reaction of 2-(*o*-aminophenyl)ethanol, indole was obtained and the yield was almost as high (90–95 %) as in the case of 2-(*o*-aminophenyl)ethanol. The catalysts and reaction conditions could be varied as shown in Table 2. The table indicates the catalysts containing copper to be of advantage as compared to those with other metals. Hydrogen was used for the reduction in most of the experiments, but other reducing gases, *e.g.* ammonia (run 12), could be used.

A typical run with copper chromite as catalyst gave indole in 90 % yield, and with the by-products given in Table 1.

**Table 1.** Formation of indole and byproducts from 2-(*o*-nitrophenyl)ethanol over copper chromite at 250°, with hydrogen [12 mol/mol 2-(*o*-nitrophenyl)ethanol] as reducing gas.

Products	Yields (%) <sup>a</sup>
Aniline	0.1
<i>o</i> -Toluidine	2.6
<i>o</i> -Aminoethylbenzene	2.1
2,3-Dihydroindole	4.4
Indole	90
Unidentified	0.8

<sup>a</sup> Determined by GLC.

The byproducts are readily accounted for by expected side reactions: retro-Knoevenagel condensation of 2-(*o*-nitrophenyl)ethanol would give *o*-nitrotoluene which would be reduced to *o*-toluidine. Dehydration of 2-(*o*-nitrophenyl)ethanol followed by hydrogenation of the *o*-nitrostyrene formed would give *o*-aminoethylbenzene, and incomplete dehydrogenation of 2,3-dihydroindole shows up in the presence of this compound. That this is the probable source of 2,3-dihydroindole and not hydrogenation of indole, was indicated by an increase in the

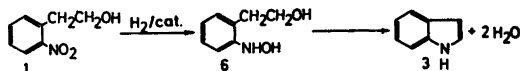
content of 2,3-dihydroindole as the catalyst aged.

One byproduct which showed up in a very low yield (less than 10<sup>-2</sup> %) was a crystalline, high melting compound, almost insoluble in common solvents. The IR spectrum indicated a strongly hydrogen bonded hydrogen to be present and the electronic spectrum that it contained a longer chromophore than indole itself. The mass spectrum indicated an elemental formula of C<sub>16</sub>H<sub>10</sub>N<sub>2</sub>. From these indications both structures 4 and 5 (or the 5H-isomers) seemed possible for the compound. Compound 4 is quindoline, synthesized by Fichter and Boehringer,<sup>9</sup> and compound 5 quinindoline, synthesized by Gabriel and Eschenbach.<sup>10</sup>



M.p. of the substance from the indole synthesis indicated it to be quinindoline (5), and comparison of the IR spectrum with that of an authentic sample<sup>10</sup> together with mixed m.p. showed the substance to be quinindoline.

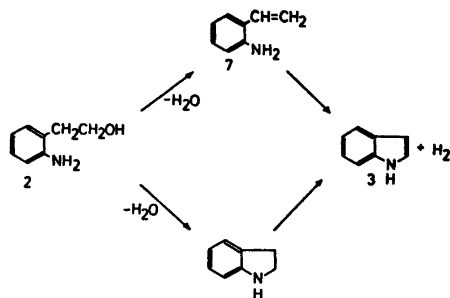
The formation of indole from 2-(*o*-nitrophenyl)ethanol (1) probably proceeds *via* 2-(*o*-aminophenyl)ethanol (2) as indicated above. However, 2-(*o*-hydroxylaminophenyl)ethanol (6) can not be excluded as an intermediate. The hydrogenation conditions used would normally give the amino compound in high yield.<sup>8</sup> However, in the present case, the hydroxylamine (6) might be trapped in the cyclization reaction before further reduction could take place.



This possibility has not been investigated further. However, because of the ready reduction of nitro aromatics to the corresponding amines<sup>8</sup> it seems reasonable to assume that at least part of the indole was formed *via* 2-(*o*-aminophenyl)ethanol.

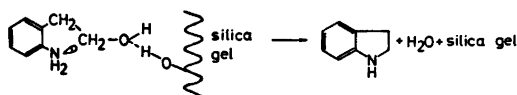
The formation of indole from 2-(*o*-aminophenyl)ethanol can be envisaged by several routes. One possibility is by *o*-aminostyrene (7) followed by cyclisation and dehydrogenation,

another by cyclisation to 2,3-dihydroindole (8) followed by dehydrogenation:



Experiments were undertaken to investigate these and other ways of formation. The route *via o*-aminostyrene was excluded by an experiment showing that this compound did not give indole at the comparatively low temperature (250°) used for the reaction of 2-(*o*-aminophenyl)ethanol.

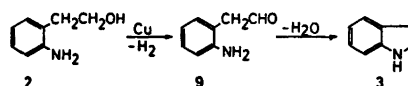
On the other hand, dihydroindole gave indole in high yield (98 %) under the reaction conditions. Further, if 2-(*o*-aminophenyl)ethanol vapour was passed over silica gel without copper metal, dihydroindole was obtained (98 % yield). This cyclisation of aminophenylethanol was shown to be catalyzed by silica gel, since no cyclisation took place over Vycor chips under the same reaction conditions. The catalytic effect of silica gel may be explained by the hydroxyl groups present.



From these results, it seemed plausible to assume that the indole had been formed by cyclisation of 2-(*o*-aminophenyl)ethanol followed by dehydrogenation of 2,3-dihydroindole.

However, another possible reaction path was revealed when metallic copper alone (from copper oxide) was used as catalyst. Again, indole in high yield was obtained from 2-(*o*-aminophenyl)ethanol. In the case of metallic copper, the catalytic cyclisation above is harder to envisage as the copper has no hydroxyl groups like silica gel.

A possible path for the formation of indole over metallic copper would be by dehydrogenation of the alcohol group of 2-(*o*-aminophenyl)ethanol to an aldehyde group. The product *o*-aminophenylacetaldehyde (9) would probably cyclize to indole under the reaction conditions.



The catalytic dehydrogenation of alcohols to the corresponding aldehydes is a well known

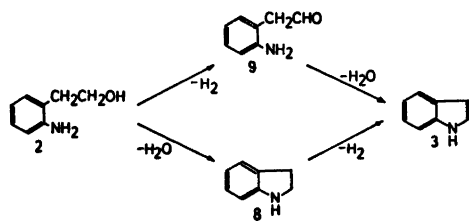
reaction:  $\text{RCH}_2\text{OH} \xrightarrow{\text{cat.}} \text{RCHO} + \text{H}_2$ .<sup>11</sup> The equilibrium is usually displaced towards the aldehyde by trapping the hydrogen formed. In the present reaction, the equilibrium would be displaced by the removal of *o*-aminophenylacetaldehyde (to indole).

To test the hypothetical reaction path *via* the aldehyde, 2-(*p*-aminophenyl)ethanol vapour was passed over silica gel and metallic copper catalysts. With 2-(*p*-aminophenyl)ethanol, no cyclization reaction would be possible, and *p*-aminostyrene was expected from the reaction over silica gel (by catalytical dehydration). From the reaction over copper it was hoped to identify traces (due to ready polymerization) of *p*-aminophenylacetaldehyde.

However, from both experiments, only unreacted 2-(*o*-aminophenyl)ethanol was isolated and in low yields, indicating polymerization of the products in the reactor. No conclusions as to presence of an aldehydic intermediate (9) in the indole synthesis could thus be drawn.

To test if an aldehyde nevertheless could be formed under the reaction conditions, 2-phenylethanol vapour was passed over copper at 250° in a nitrogen stream. The main product was indeed phenylacetaldehyde (50 % yield). Maihle<sup>12</sup> had earlier obtained phenylacetaldehyde from 2-phenylethanol over copper at 300°. Our result thus indicates that the copper catalyzed synthesis of indole from 2-(*o*-aminophenyl)ethanol might proceed *via o*-aminophenylacetaldehyde.

The reaction path *via* 2,3-dihydroindole was obviously not excluded by the results, and the only conclusion possible was that the reaction might proceed by both paths.



By the method presented here, it has thus been possible to synthesize indole in one step and in high yield from 2-(*o*-nitrophenyl)ethanol. This should be compared to the three steps necessary if a synthetic route in liquid phase is used.<sup>1</sup> On the other hand, the synthesis in liquid phase is probably more advantageous for the synthesis of substituted indoles.<sup>6</sup> The presented synthesis in vapour phase has not yet been investigated in the case of substituted indoles.

## EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer Model 257 and the electronic spectra on a Beckman DK-2 spectrophotometer. Gas chromatographic separations were made on a Perkin-Elmer F-11 gas chromatograph, equipped with a hydrogen flame ionisation detector and a 10% SE-30 column. Mass spectra were recorded on an A. E. I. M. S. 902 mass spectrometer.

The gas phase reactor was made of a 60 cm long Vycor tube (o.d. 18 mm) equipped with a thermocouple well (o.d. 8 mm). The reactor was heated in an electrically heated fluidized bed with silicon carbide as heat transferring medium.<sup>13</sup> The reactor was half filled with catalyst (catalyst volume 30 ml) and the rest of reactor filled with Vycor chips (to heat reactants before reaching the catalyst). The liquid reactants were passed onto the top of the reactor by a syringe pump, together with the appropriate gas. The effluents from the reactor were analyzed by GLC. The stated percentages of the various components in the reaction mixtures were calculated from the gas chromatograms after corrections had been made for differences in the ionizing power of the various components.

**Reactions of 2-(*o*-aminophenyl)ethanol in the vapour phase. Indole synthesis.** When the experiment of Ufer *et al.*<sup>7</sup> was reproduced, indole was formed in 70% yield during the first 10 min. The catalyst deteriorated rapidly, and later indole was found in low yield together with 2,3-dihydroindole and unreacted starting material. The reaction was then tried with a catalyst made by soaking silica gel in an aqueous solution of copper nitrate, evaporating the water, drying

the silica gel at 100°, heating it at 250° until the evolution of nitrous gasses ceased and finally reducing it with hydrogen at 250°. The catalyst contained 7% copper. With this catalyst (30 ml) in the reactor, 2-(*o*-aminophenyl)ethanol (10 g/h) was evaporated in a stream of hydrogen (200 ml/min) and passed over the catalyst. The yield of indole was 95% and the main byproducts were 2,3-dihydroindole (2%) and *o*-aminoethylbenzene (1.5%). The indole from the reactor was 96% pure and had m.p. 45–47°. Several commercial copper or copper chromite catalysts were tried and gave essentially the same result. The working lives of the catalysts were several hundred hours. A copper metal catalyst made by hydrogen reduction of copper oxide (Merk AG, Kupferoxid Draht Form) gave the same result.

**2,3-Dihydroindole from 2-(*o*-aminophenyl)ethanol.** 2-(*o*-Aminophenyl)ethanol (10 g/h) and hydrogen (200 ml/min) were passed through the reactor containing silica gel as catalyst at 250°. The yield of 2,3-dihydroindole was 98%.

**Gas phase reaction of 2-(*o*-aminophenyl)ethanol without catalyst.** This reaction was carried out as the previous one, except that the reactor was filled with Vycor chips alone. The product consisted of unreacted starting material. No 2,3-dihydroindole was detected.

**Gas phase reaction of *o*-aminostyrene.** *o*-Aminostyrene (10 g/h, prepared by reduction of *o*-nitrostyrene with iron turnings) together with hydrogen (200 ml/min) was passed through the reactor containing silica gel (30 ml) as catalyst at 250°. The product consisted of unreacted *o*-aminostyrene. No 2,3-dihydroindole was detected. When 7% copper on silica gel was used as catalyst, *o*-aminoethylbenzene was obtained in 97% yield.

**Gas phase reaction of 2,3-dihydroindole.** When 2,3-dihydroindole was vaporized and passed with hydrogen over the copper/silica gel catalyst, as described for 2-(*o*-aminophenyl)ethanol, indole was obtained in 98% yield.

**Reactions of 2-(*p*-aminophenyl)ethanol in the vapour phase.** 2-(*p*-Aminophenyl)ethanol (2.5 g) was dissolved in 1,2-dimethoxyethane (37.5 g) and the solution (19.6 g/h) pumped into the reactor at 250° together with N<sub>2</sub> (30 ml/min). When silica gel (30 ml) was used as catalyst, 21.10 g solution was reacted (containing 1.9 g *p*-aminophenylethanol).

The product (0.1 g concentrated, 5% of starting material) gave 8 peaks on GLC, one of which was possibly 2-(*p*-aminophenyl)ethanol. By extracting the catalyst for 6 h with a 1:1 mixture of chloroform:methanol, 0.3 g of a product consisting mainly of starting material (as judged by TLC) was obtained.

When copper metal (from copper oxide) was used as catalyst and the other conditions retained as described above, 31.5 g of the *p*-aminophenylethanol solution (containing 2.06 g of *p*-aminophenylethanol) was reacted. A certain amount of product was isolated (ca. 450 mg),

consisting mainly of unreacted starting material, (GLC).

As the conditions for the reactions of *p*-aminophenylethanol (due to the crystallinity of the substance) were slightly different from those originally used for *o*-aminophenylethanol, control experiments were run: A solution of 2-(*o*-aminophenyl)ethanol (3.5 g) in 1,2-dimethoxyethane (50 g) was reacted at the same rate and under the same conditions as those for the *p*-isomer described above. When silica gel was used as catalyst, 2,3-dihydroindole was obtained. When copper was used as catalyst, indole was the product. Both substances were obtained in the same yields and purities as described for the reaction without solvent and with H<sub>2</sub> as carrier gas.

**Formation of 2-phenylacetaldehyde.** 2-Phenylethanol (1.85 g/h) was pumped into the reactor at 250° together with nitrogen (85 ml/min). The reactor contained copper (from copper oxide) (13 ml) and Vycor chips (10 ml). Totally 3.7 g of phenylethanol was reacted. The condensate from the reactor (3.05 g) contained phenylacetaldehyde (35 %), ethylbenzene (26 %), and phenylethanol (31 %) (analyzed by GLC, internal standard method). This corresponded to a yield of phenylacetaldehyde of 50 % (calculated on basis of reacted alcohol). Phenylacetaldehyde

was identified after isolation by column chromatography, by comparison of IR and TLC with those of an authentic sample.

**Indole from 2-(*o*-nitrophenyl)ethanol.** 2-(*o*-nitrophenyl)ethanol (5.6 g/h) was pumped into the reactor containing 30 ml of catalyst and 30 ml of Vycor chips together with a reducing gas. The products were analyzed by GLC. Results and reaction conditions are given in Table 2. From the reaction mixture with copper chromite as catalyst, 0.01 % of a crystalline compound was isolated. The compound had mp. 341–343°, IR (KBr) 3140 (broad, from 3300 to 2300 cm<sup>-1</sup>), 1640, 1610, 1580, 1490, 1480, 1460, 1410, 1330, 1280, 1260, 1230, 1130, 1020, 990, 950, 910, 880, 860, 820, 790, 760, 740, 700, 640 cm<sup>-1</sup>. The electronic spectrum (in ethanol) had maxima (in nm) numbers in parantheses give  $\epsilon_{\text{max}}$  (l mol<sup>-1</sup> cm<sup>-1</sup>): 368 (3600), 331 (17 000), 317 (12 000), 270 (52 000), 265 (shoulder) (45 000). The mass spectrum indicated an elemental formula of C<sub>12</sub>H<sub>10</sub>N<sub>2</sub> with the molecular ion giving the base peak.

The isolated compound was in every respect identical with an authentic one synthesized by the method of Gabriel *et al.*<sup>10</sup> (In the synthesis,<sup>10</sup> catalytic reduction was used instead of the sulfide reduction used by these authors).

Table 2. Synthesis of indole from 2-(*o*-nitrophenyl)ethanol (ONPE) in the vapour phase, (5.6 g ONPE/h reacted). Reducing gas H<sub>2</sub>.

Run	Catalyst	Reaction temperature °C	Mol reducing gas/mol ONPE	Yield of indole %
1	7 % Cu/silica gel	250	12	99
2		330	12	66
3		400	12	26
4		250	3	70
5		250	18	97
6	7 % Cu/Al <sub>2</sub> O <sub>3</sub>	250	6	97
7	7 % Ni/silica gel	250	12	59
8	7 % Co/silica gel	250	12	78
9	0.5 % Pd/C	250	3	66
10	Cu (from CuO)	250	12	95
11	V <sub>2</sub> O <sub>5</sub> /K <sub>2</sub> SO <sub>4</sub> -silica gel	250	12	85
12	V <sub>2</sub> O <sub>5</sub> /K <sub>2</sub> SO <sub>4</sub> -silica gel	250	12 <sup>a</sup>	84
13	Copper chromite	250	12	90

<sup>a</sup> Reducing gas NH<sub>3</sub>.

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