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Investigation into the synthesis of Indazole

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INVESTIGATION INTO THE SYNTHESIS OF INDAZOLE

by

Max Peter Dreyfuss

A thesis presented to the Department of Chemistry of Union College in partial fulfillment of the requirements for the degree of Bachelor of Science with a Major in Chemistry.

By Max Peter Dreyfuss

Approved by Howard E. Wolfson

Date May 24, 1952
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INTRODUCTION

These investigations were undertaken in order to study the effect that various acyl or aroyl groups on o-toluidine

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{N} \quad \text{C} \quad \text{R} \quad \text{C} \quad \text{R} \\
& \quad \text{N} \quad \text{H} \quad \text{R} \quad \text{C} \\
& \quad \text{N} \quad \text{H} \\
\end{align*}
\]

have on the yield of indazole, when the latter is prepared by the methods of Barclay, et. al. (1) as modified by Rzeszotarski (23). In addition further information on the mechanism of the reaction and on the structure of indazole was sought from these data.

Indazole has, as yet, no commercial applications and is not (to the author's knowledge) produced by any large chemical concern. A practical grade of the 5-nitro derivative, however, is produced by the Eastman Kodak Co. for sale and for use by them in film.

The early workers (11) designated the formula I as

\[
\begin{align*}
\text{I} & \\
\text{II} & \\
\text{III} & \\
\text{IV} & 
\end{align*}
\]

indazole and II as isocindazole. Several modern reference works (7) (19) list III as indazole and II as isocindazole.

Barclay, et. al. state that by analogy with other heterocyclic compounds there can be little doubt that indazole and its derivatives are resonance hybrids, the resonance being largely due to that of the benzene nucleus. I believe that
Barclay confuses the terms 'resonance' and 'tautomerism'. Tautomerism more accurately describes the phenomenon. On the other hand, Hayes and Hunter (12) state that the old distinction between indazole and isoindazole is now invalid, the imino-hydrogen atom not being definitely located on either nitrogen atom, but two isomeric N-substituted indazoles are distinguishable. 2-methyl indazole, according to Barclay, must have the general structure of either I or III and gives some evidence he found which favors the quinoid structure. (III)

For purposes of writing and explaining reactions in this paper, indazole will be written and numbered as in IV, with the understanding that it is only one of the contributing forms.
HISTORICAL

Indazole was discovered by E. Fischer and Kuzel (9) in 1883. These workers and also E. Fischer and Tafel (10) performed the earliest studies on the synthesis of indazole. They noticed that 2-hydrazonecinnamic acid easily lost acetic acid to form indazole (20):

\[
\text{Ph-}C\equiv C-CO\text{H} \rightarrow \text{Ph}-N\equiv N-NH_2 + \text{C}_2\text{H}_5\text{COOH}
\]

Heusler (14) obtained a slight yield of indazole by the reaction of toluol-diazo-toluide with acetic anhydride:

\[
\text{Ph-N\equiv N-NH}_2 + \text{CH}_3\text{-C\equiv CO} \rightarrow \text{Ph-N\equiv N-NH}_2 + \text{CH}_3\text{-C\equiv CO}
\]

E. Noelting (21), while investigating the synthesis of substituted indazoles, made indazole from o-toluidine, through the diazonium salt which was allowed to hydrolze and couple into indazole:

\[
\text{Ph-}N\equiv N-NH_2 + \text{NaNO}_2 \rightarrow \text{Ph-N\equiv N-N}_2\text{Cl} + \text{HCl} \rightarrow \text{Ph-N\equiv N-NH}_2
\]

Noelting's best yield in several runs was 2.9%. This synthesis was further studied by Rzeszotarski (23). He obtained no indazole, but did obtain considerable data on products obtained under varying acidic conditions.

The method which was essentially used in this work was developed by Jacobsen and Huber (18), modified by Barkley, et. al. (1) and Rzeszotarski (23). The starting material was N-benzoyl-o-toluidide, which was reacted with nitrous fumes
in acetic acid-acetic anhydride solvent to form the N-nitroso derivative which, when allowed to stand overnight dissolved in benzene, yielded indazole and benzoic acid:

Barclay reported a yield of 8.9%, while Rzeszotarski obtained 34.6% when Barclay's procedure was modified slightly.

After the synthesis was attempted unsuccessfully with the N-acetyl derivative of o-toluidine, an attempt was made to duplicate Rzeszotarski's synthesis. A good deal of trouble was had with the nitrosation step and it was only after several weeks of research when some successful further modifications were made, that the reaction was carried out successfully. However, the yield obtained was only 20.5%.

With these modifications, the nitrosation of the other derivatives proceeded readily and a 38.1% yield of indazole was noted with one of the derivatives.

In view of the high yield attainable and the relatively common ingredients used, it appears that basically Barclay's method for the synthesis of indazole is still the simplest and most practical known at the present time.
APPARATUS

The synthesis of indazole did not suffer from the disadvantage of the use of complicated or special apparatus. A rheostat-controlled mechanical stirrer was used for a while, but it was found to be as satisfactory, if not more so, to use no stirrer and only hand stirring in the few instants requiring it. The reactions were all carried out in beakers or flasks. A simple distillation set up was the most complicated set up required.

The gas generator for the nitrous fumes was constructed from a one liter grignard flask. Through one opening a dropping funnel admitted dilute sulfuric acid. The outlet passed to a tube, placed underneath the surface of the solution being nitrosated. A 250 ml Erlenmeyer flask served as a trap between the gas generator and the gas inlet to the solution being nitrosated. Rubber stoppers were used (the fumes attacked cork stoppers). The apparatus was air tight.

The tube used to admit the nitrous fumes below the surface was, at first, merely a glass tube. It was later found more satisfactory to use a sintered glass gas delivery tube. Its use resulted in the admission of smaller gas bubbles which bubbled up through the solution more slowly and thus presented greater opportunity for reaction.
Preparation of N-acetyl-o-toluidide

This derivative was prepared according to the synthesis given for acetanilide by Fieser (9).

o-Toluidine (107 gm.) was added to 2500 ml water and 83 ml concentrated hydrochloric acid. The reddish solution, colored from oxidation impurities in the o-toluidine, was rendered colorless by stirring with 15 grams charcoal and filtering. The solution was then heated to 50°, 116.5 ml acetic anhydride was added, and stirred until almost dissolved. Then 150 grams of sodium acetate in 500 ml. water was added immediately. The mixture was stirred, cooled in an ice bath and the crystals which separated were collected and dried. A 102.5 gram (68%) yield of white crystals, m.p. 108° (110° lit.) was obtained.

Preparation of N-benzoyl-o-toluidide

This derivative was prepared by the Schotten-Baumann reaction according to the procedure given by Rzeszotarski (23).

o-Toluidine was distilled over zinc dust in order to remove it from the colored oxidation products. Twenty grams were made alkaline and 21.5 ml (26.2 gm.) benzoyl chloride were added in five ml portions in a 250 ml. glass stoppered Erlenmeyer flask. The solution was shaken vigorously, maintained alkaline and cooled after each addition. After all of the benzoyl chloride had been added, the flask was shaken
until no more heat was emitted. The product was filtered, washed with cold water and recrystallized twice from ethanol. In some preparation it was only recrystallized once. Yields from 53-66% were obtained in the several preparations, m.p. 144-146° (145-146° lit.)

Preparation of other derivatives of O-toluidine

N-(m-nitro benzoyl)-o-toluidide, m.p. 144-150°; N-benzene sulfon-o-toluidide, m.p. 123-125°; N-chloroacetyl-o-toluidide, m.p. 104-105°; N-(β-naphthoyl)-o-toluidide, m.p. 130-135°; and N-isocaproyl-o-toluidide, m.p. 75.5-76.5 were prepared by Schotten-Baumann reaction according to the procedure above.

These derivatives were all prepared by chemistry students taking organic chemistry. It was only through their efforts that this research could be carried as far as it was, and their work in preparing these derivatives was greatly appreciated.

Attempted preparation of N-nitroso-N-acetyl-o-toluidide

The nitrosation of this derivative was attempted in accordance with the modification Rzeszotarski had made on Barclay's procedure, using the N-benzoyl derivative. Fifteen grams (0.1 mole) was dissolved in a mixture of 90 ml of acetic acid and 20 ml acetic anhydride by heating to 70° in a one liter Grignard flask. The mixture was cooled with stirring in an ice bath to 10°, resulting in a slight amount of crystallization.
A gas generator was made from a one liter Grignard flask with one inlet for dilute sulfuric (6 N) acid through a dropping funnel and an outlet through a safety bottle into the reaction flask. The flask was charged with sodium nitrite and the acid was allowed to trickle in slowly. After the system was cleared of the brown fumes resulting from oxidation by air, the outlet was placed under the surface of the solution of toluidine and the flow of sulfuric acid regulated so that 2-3 bubbles of nitrous fumes passed into the reaction flask per second. A glass tube connected to a water pump was placed in one of the openings of the reaction flask to withdraw the brown nitric oxide fumes formed by the oxidation of excess nitrous fumes.

The admission of gas was continued for 1 1/2 hours, resulting a light green solution. The solution was poured into a mixture of 100 ml water and 100 grams ice, resulting not in the expected separation of a solid or oil, but in a clear light green solution. Apparently no significant amount of the nitroso derivative had been formed. It was thought, however, that it may be in solution, so some time was spent in attempting to separate the product in following runs by vacuum distillation. It is seen now that any nitroso derivative present would have been decomposed even at the heat of vacuum (water pump) distillation.
Preparation of N-nitroso-N-benzoyl-o-toluidide

At this point it was decided to attempt to duplicate Rzeszotarski's synthesis and yield. Twenty grams (0.098 moles) of N-benzoyl-o-toluidide were dissolved in 90 ml acetic acid and 20 ml acetic anhydride at 60° and cooled to 10° with rapid stirring, resulting in a slurry of fine crystals. Nitrous fumes were admitted for two hours, after which time the slurry was still quite thick and no noticable reaction had occurred (a clear green solution marks the completion of the reaction.) Mechanical stirring seemed essential, so it was attempted again with mechanical stirring, but still the reaction could not be made to go after several trials.

The reaction was now attempted on a test tube scale using one gram at a time of the N-benzoyl derivative and suitable quantities of solvents. The reaction worked when the gas delivery tube was pulled out to a capillary but no success resulted when this was attempted on twenty grams. (At this time a glass tube was still being used to admit the nitrous fumes.) One gram samples were now tried in various solvents and solvent mixtures. One sample was made to react in acetic acid-acetic anhydride by the addition of two drops of o-toluidine. A certain degree of success was also noted using pyridine as solvent. One gram of the derivative was then dissolved in 3 ml acetic acid, 2 ml acetic anhydride and 0.5 ml pyridine by heating. Ten minutes of nitrosation of the cooled slurry yielded a clear green solution which
gave a yellow precipitate on pouring into ice water. This precipitate gave the characteristic "flash" on heating (13) (23), and had a melting point of about 60°. Equal success was obtained when the reaction was run with five grams and a suitable ratio of solvents. The nitroso derivative was allowed to react in benzene and a small amount of indazole, m.p. 146-148°, was isolated.

During the test tube trials the gas generator was charged with a solution (250 grams in 300 ml water) of sodium nitrate instead of the solid compound. In this way it was possible to obtain a smoother and easier regulated flow of gas. This method was used from then on.

Twenty grams (0.098 moles) of the N-benzoyl derivative were dissolved in 60 ml acetic acid and 40 ml acetic anhydride in a 250 ml electrolytic beaker. Nitrous fumes were added through the sintered glass gas delivery tube. The electrolytic beaker was used to confine the solution to a narrow column, so that the gas would bubble through a greater height of solution and also to allow the use of the gas delivery tube, which was impractical in the Grignard flask.

The gas delivery tube was used for reasons already mentioned.

During this run it was found that mechanical stirring was unnecessary in the electrolytic beaker and that occasional hand stirring was sufficient. The gas bubbling through the slurry accomplished some stirring also. Hereafter, mechanical stirring was no longer used.
Nitrous fumes were added to the slurry at 10° for one hour, the slurry turned green but showed no signs of clearing. Nine ml of pyridine were then added and the nitrosation continued for another hour, in which time the slurry became a clear, light green solution. When poured into the ice water an oil separated which soon solidified. The solid nitroso derivative was collected, washed free of acetic acid odor and allowed to dry at room temperature for a half hour. The solid melted at 66° (decomposition) (62-63° lit.) and gave a flash on heating. The solid was put in a glass stoppered Erlenmeyer flask, covered with 150 ml of sodium dried benzene and allowed to stand over the weekend. On the next morning a dark red homogeneous solution was noted.

As the nitroso derivative was not dry when put into benzene solution, there was a small layer of water underneath the red solution which was separated and discarded. The solution was refluxed for 5-10 minutes and then 100 ml benzene were distilled off. The remaining solution on cooling was washed with 50 ml saturated sodium carbonate solution yielding an orange precipitate which was collected and washed. The precipitate was partially dissolved in dilute (6 N) hydrochloric acid, forming two layers—a lower clear reddish layer and an upper red oily layer. The lower layer when neutralized with 10% sodium hydroxide gave a fine gray precipitate which when collected and air dried for two days weighed 4.1 grams. The gray precipitate was recrystallized twice from about 150 ml water, filtering the hot solution. The crystals weighed 2.3
grams after drying at 100-110° for one hour, representing a 20.5 % yield of indazole from benzoyl-o-toluidide as the starting material. The melting point was 146-149° (lit. 148°). A mixed melting point with the starting product (m.p. 144-146°) was 110-117°, confirming that the product was not starting material. The crystals, however, were of poor shape and still somewhat yellowish.

**Indazole from N-acetyl-o-toluidide**

Fifteen grams (0.1 moles) of the N-acetyl derivative was dissolved in 60 ml acetic acid, 40 ml acetic anhydride and 9 ml pyridine without heating and the solution cooled to 10°. The greenish-yellow clear solution resulting after an hour of nitrosation was poured into ice water yielding a yellowish oil which did not solidify. The oil smelled strongly of acetic acid and anhydride and was washed twice with water in an unsuccessful attempt to remove the odor. When heated, a drop of the oil distinctly flashed.

The oil was completely miscible in benzene and on standing overnight resulted in a dark red solution. The indazole was separated and purified as above, yielding 2.0 grams of a rather yellow crystal melting at 145-148°. This represented a 17.0 % yield of indazole.

**N-(m-nitrobenzoyl)-o-toluidide**

Twenty grams (0.078 moles) of this derivative were dissolved in the same amounts of solvent as above by heating to 85°. A thick slurry resulted on cooling to 10°. The slurry had turned green but had not cleared after two hours of
nitrosation. The slurry was filtered and the filtrate drowned in water. The resulting precipitate was collected and allowed to stand in benzene overnight, the remaining precipitate was also allowed to stand in benzene (separately). Neither precipitate gave a flash on heating.

Both benzene solutions were red on the next morning and both contained precipitate. The two solutions were combined after separating from the precipitate. The concentrated benzene solution yielded no precipitate on washing with saturated sodium carbonate. It would appear that only a small amount of nitroso derivative was formed and none of this formed indazole. No effort was made to identify the tarry red oil remaining after the benzene had completely evaporated.

N-benzene sulfon-o-toluidide

The same amounts of solvents were used to dissolve 25 gms (0.10 mole) at 60°. A reddish slurry was obtained on cooling at 10°. After 45 minutes of nitrosation the slurry cleared to a yellowish solution, which yielded a viscous oil on pouring into ice water. The oil did not flash on heating but decomposed into a black tar. The benzene solution of the oil darkened only slightly on standing overnight. The fumes over the solution turned brown on exposure to air and on refluxing the solution, large quantities of brown fumes were evolved. Nevertheless benzene was distilled off, but no precipitate was obtained on washing the remainder with carbonate. An oil did separate, however, which solidified on acidification
and after recrystallization with alcohol-water had a m.p. of 110-113°. A solid also separated from the remaining benzene solution which gave a m.p. of 110-115°. A little of this solid when recrystallized from alcohol had the pinkish appearance of the starting material. In addition both of these solids starting and the material were soluble in 10% sodium hydroxide and insoluble in dilute acid solution. These facts confirmed the suspicion that the nitroso derivative was decomposing into the starting material (m.p. 123-125°) when the brown fumes were given off.

**N-chloroacetyl-o-toluidide**

Ten grams (0.054 moles) were dissolved in one half the usual amounts of solvents rather easily forming a dark clear solution, forming no precipitate on cooling. One hour of nitrosation caused no significant changes in the appearance of the solution. On pouring into ice water (50 ml plus 50 gms ice) a dark oil separated which solidified, but seemed to melt at about room temperature. Because of this low melting point the precipitate was not dried but immediately covered with benzene (75 ml) forming a dark red solution. The solid gave a flash on heating.

No precipitate was obtained when the remaining benzene solution was washed with saturated sodium carbonate. The benzene was allowed to evaporate leaving a dark sticky oil which had an uncorrected boiling point of 245-250°. An attempt was made to show that this product was 2-methyl diphenyl,
by oxidizing it to 2-phenyl benzoic acid with potassium permanganate (5) (17). A reaction seemed to occur with the permanganate as there was frothing and no oily substance remained, however, no soluble products seemed to result as no precipitate resulted on acidification of the filtrate which had been separated from the manganese dioxide. The oil was insoluble in water, dilute acid and dilute alkali and was soluble in concentrated sulfuric acid.

\[
\text{N-}(\beta\text{-naphthoyl})\text{-o-toluidide}
\]

Nineteen and six tenths grams (0.075 moles) were dissolved in 60 ml acetic acid, 40 ml acetic anhydride and 10 ml pyridine at 75°. A thick white slurry resulted on cooling to 10° with rapid stirring, which became greenish yellow after one hour of nitrosation. Ten more ml of pyridine were added and nitrosation continued for another half hour but the slurry did not go into solution. Nevertheless, the slurry was drowned in ice water resulting in a yellow precipitate which flashed and suddenly decomposed in a capillary tube at 90°.

On standing overnight the benzene solution became red and contained a good deal of precipitate which was filtered off and washed with benzene. When dry the precipitate weighed about 9 grams, was soluble in sodium carbonate and sodium hydroxide, insoluble in dilute hydrochloric acid and melted at 175-180°. It was concluded that the precipitate was \(\beta\)-naphthoic acid (m.p. 180-181 lit.)

The orange precipitate formed in the concentrated benzene
solution on washing with saturated sodium carbonate, was partially dissolved in dilute acid. There was some solid remaining which would not dissolve and which was shown later to be largely $\beta$-naphthoic acid. The acid solution when neutralized yielded a yellowish precipitate which was collected and redissolved in 30 ml acid. This yellow solution was decolorized by stirring with about a gram of activated charcoal and filtering. The filtrate was now colorless and yielded a white precipitate on neutralization. After recrystallizing once from 150 ml water and drying, the white needle-like crystals weighed 3.22 grams and melted at 146-149$^\circ$. This represented a 36.3% yield of indazole from $\beta$-naphthoyl-$o$-toluidide.

**N-isocaproyl-$o$-toluidide**

Twenty and a half grams (0.01 mole) was dissolved in a 60-40-10 ratio of solvents at 60$^\circ$. The dark red clear solution which resulted on cooling to 10$^\circ$, was nitrosated for 1½ hours. Little visible change had occurred to the solution which yielded an oil on drowning in ice water. The oil was separated into the glass stoppered flask. Oil in suspension in the water and oil adhering to the sides of the separatory funnel was collected by extracting with benzene. The oil flashed rather violently when heated.

When the remaining benzene solution was washed with carbonate a large amount of carbon dioxide was given off. The carbonate layer yielded a yellow oil, which was probably
isocaproic acid, on acidification. The orange precipitate when dissolved in dilute acid formed an upper dark red oily layer and a lower red aqueous layer. The aqueous layer was treated with charcoal twice resulting in a clear slightly yellow solution. On neutralization a white precipitate was obtained which when recrystallized and dried, weighed 4.49 grams and melted at 146-148\(^\circ\) C. This 38.1 % yield of indazole represented the best obtained from any of the derivatives attempted.
<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Melting Point °C</th>
<th>Product of Nitroso Derivative in benzene</th>
<th>Yield in Grams</th>
<th>Yield %</th>
<th>Melting Point of Product °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-benzyloctoluidide</td>
<td>144-146</td>
<td>Indazole</td>
<td>2.3</td>
<td>20.5</td>
<td>146-149</td>
</tr>
<tr>
<td>N-acetyloctoluidide</td>
<td>108-110</td>
<td>Indazole</td>
<td>2.0</td>
<td>17.0</td>
<td>145-148</td>
</tr>
<tr>
<td>N-(m-nitrobenzoyloctoluidide</td>
<td>144-150</td>
<td>Little nitroso derivative formed. Starting Material</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>N-chloroacetyloctoluidide</td>
<td>104-105</td>
<td>2-methyl diphenyl (?)</td>
<td>??</td>
<td>??</td>
<td>146-149</td>
</tr>
<tr>
<td>N-β-naphthoyloctoluidide</td>
<td>130-135</td>
<td>β-naphthoic acid approximately 9</td>
<td>3.22</td>
<td>36.3</td>
<td>175-180</td>
</tr>
<tr>
<td>N-isocaproyloctoluidide</td>
<td>75-76</td>
<td>Indazole</td>
<td>4.49</td>
<td>38.1</td>
<td>146-148½</td>
</tr>
</tbody>
</table>
DISCUSSION

Solvents

Barclay (1) in his preparation of N-nitroso-benzoyl-o-toluidide used 50 ml each of the acetic acid and anhydride and ran the reaction at 40°. Rzeszotarski (23) was able to obtain the nitroso derivative by this method, but was unable to obtain the decomposition in benzene to indazole until he changed the ratio of acid to anhydride to 90 ml to 20 ml and changed the temperature of nitrosation to 10°. However in several attempts it was found impossible to make the nitrous fumes react with either acetyl- or benzoyl-o-toluidide in the 90 to 20 mixture at 10°. The action of pyridine may in part be a solvent action. The benzoyl derivative, as evidenced by the rather thick slurry, is not very soluble in the solvent mixture. The nitrous fumes react with the little that is in solution forming the more soluble nitroso derivative and allowing more of the benzoyl toluidide to dissolve. Completion of the reaction is noted by the clearing of the solution. The addition of pyridine caused the slurry to thin considerably.

However, the acetyl derivative is quite soluble in the solvent mixture and yet the nitroso derivative was not formed until pyridine was added. It would seem then that the primary action of pyridine on the nitrosation reaction is as a catalyst. In one of the test tube runs the nitrosation was made to go successfully by the addition of two drops of
o-toluidine. Perhaps o-toluidine is also a catalyst for the reaction, in which case the careful purification of the derivatives is unnecessary, in fact detrimental. Rzeszotarski's erratic results in obtaining reaction with nitrous fumes may be accounted for by the presence or absence of small amounts of o-toluidine.

The purpose of the acetic anhydride is to lower the freezing point of the acetic acid below the temperature at which the reaction is carried out.

Nitrosation

Only with two of the reactants (benzoyl- and benzene sul fon-o-toluidide) was it possible to determine the completion of the nitrosation reaction by the dissolution of a slurry. In the case of the three soluble reactants (acetyl-, chloroacetyl-, and isocapryl-o-toluidine) the nitrosation was continued for about the length of time it took for the partially soluble reactant, benzoyl toluidide, to clear (about an hour.) At the end of an hour a few drops of the solution were put into 20 ml of water. If only an oil separated, rather than a white precipitate, it was assumed that the reaction was complete. In one case, β-naphthoyl-o-toluidide, the nitroso derivative seemed to be as insoluble as the starting material. The only change noted was a change in the color of the slurry from white to yellow. However, a change in color from white to greenish-yellow also occurred with the benzoyl derivative before the slurry cleared. In
another case, m-nitrobenzoyl-o-toluidide, the slurry did not clear, but here it was found that little or no nitroso derivative had formed.

Purification of Indazole

The first two yields of indazole were colored slightly yellow. The second recrystallization was found to improve the color very little, so, since recrystallization reduced the yield considerably, further recrystallizations to remove the color were not attempted. The third time indazole was obtained it was decided to attempt to remove the color while the indazole was in acid solution. This was done successfully with activated charcoal and white crystals were obtained after one recrystallization. For the formation of fairly large needle like crystals, it was found essential to allow the hot solution of indazole in water to cool slowly (in air) and not to use an ice bath until the solution had reached room temperature.

Reaction of nitroso derivatives in benzene

Hayworth and Hey (13) divide acylaryl amines into four groups:

Group A: Acylarylamines which yield N-nitroso derivatives of the normal kind (i.e. those which react with benzene to give off nitrogen):

\[ R-N-CO+ \overset{\text{C}}{\text{C}}-R' \overset{\text{C}}{\text{C}}H_2 \rightarrow R-C_6H_5 + N_2 \uparrow + R'COOH \]
Group B: Acylarylamines which yield abnormal N-nitroso derivatives (i.e. those which do not react with benzene but instead decompose or react intramolecularly):

\[ R-N\text{NO}_2 \overset{\text{C}_6\text{H}_6}{\longrightarrow} R-NH-\overset{\text{C}_6\text{H}_6}{\longrightarrow} R-NH-CO-R' + NO \]

Group C: Acylarylamines that react with nitrous fumes but do not give N-nitroso derivatives. Benzoyl-2-toluidide belongs to this group.

Group D: Acylarylamines which give no reaction with nitrous fumes.

Of the acylarylamines studied, most seem to belong to Group B. It would seem advisable to divide group B into two sub-groups --Group B-1, those which decompose in benzene and Group B-2, those which react intramolecularly in benzene. Acetyl-, benzoyl-, α-naphthoyl- and isocaproyl-o-toluidine, which reacted in benzene to form indazole, belong to Group B-2. Benzene sulfon-o-toluidide, which decomposed in benzene, belongs to Group B-1.

Chloracetyl-o-toluidide seemed to belong in Group A, although this was not definitely established. m-Nitrobenzoyl-o-toluidide seemed to belong in Group D, which might be expected since Hayworth and Hey reported m-nitrobenzanilide as belonging to this group.

On several occasions a slight evolution of gas which was unaffected by air was observed coming from the benzene solutions after the nitroso derivative had been dissolved for
about an hour. This was observed even in the cases when indazole was obtained. The gas was most probably nitrogen and indicated that some of the Group A type reaction was occurring, forming as a by-product of the reaction yielding indazole some 2-methyl diphenyl.

**Mechanism**

Hey and Waters (15) have formulated the reaction of N-nitroso acetonilide in benzene as follows:

\[
\begin{align*}
N^+ - C - CH_3 & \xrightleftharpoons{\text{fast}} N = N - O - C - CH_3 \\
& \rightarrow \cdot + N_2 + \cdot OC - CH_3
\end{align*}
\]

\[
\cdot + \cdot \rightarrow \text{Cyclopentadiene} + H^.
\]

\[
CH_3 \cdot + O_2 + H^. \rightarrow CH_3COOH
\]

The decomposition here was considered to be a free radical process. R. Huisgen and co-workers (24) however, have shown that the rate determining step is the isomerization and that the reaction followed first order kinetics. He further showed that the decomposition of the diazo ester was a very rapid reaction and that the rate of isomerization was independent of the solvent used. This indicated that the rate controlling process was an intramolecular one and not a reacylation. The following cyclic mechanism was proposed:

\[
\begin{align*}
N^+ - C - CH_3 & \xrightarrow{\text{slow}} \text{Cyclopentadiene} \\
& \rightarrow N = N - O - C - CH_3
\end{align*}
\]

\[
\text{[Reaction with benzene]} + N_2 + CH_3COOH
\]
The rate of the reaction was followed spectrophotometrically using a rapid azo coupling reaction to form the azo dye:

\[
\begin{align*}
\text{N=N-O-C-CH}_3 & \quad \xrightarrow{\text{spectrophotometrically}} \quad \text{N=N-} \\
\end{align*}
\]

Huisgen found that substituents on the m- and p- positions of the benzene ring only influenced the rate of rearrangement slightly, but an o- substituent caused the rate to become 1/6 the usual value. The ultimate fate of the unstable trans diazo ester depends on the nature of the solvent and other molecules present.

This work suggests the following mechanism for the formation of indazole from N-nitroso acyl- and aroyl-o-toluidides:

\[
\begin{align*}
\text{N-N=O-C-R} & \quad \xrightarrow{\text{C}_6\text{H}_6} \quad \text{N=N-} \\
\end{align*}
\]

with:

\[
\begin{align*}
\text{N=N-O-C-R} & \quad \xrightarrow{\text{C}_6\text{H}_6} \quad \text{CH}_3 + \text{N}_2 + \text{RCOOH} \\
\end{align*}
\]

as a side reaction.
For future work it is suggested that the yield of indazole obtained from succinyl- and phthalyl-di-o-toluidide and perhaps from propionyl-o-toluidide be investigated. It would also be interesting to note the effect on the yield of indazole of allowing the nitroso derivatives to decompose in benzene at temperatures of 5-10°, instead of at room temperature.
SUMMARY

1. Modifications of Reesszotarski's solvents resulted in successful preparation of N-nitroso derivatives of acylarylamines.

2. The effect that several N-substituted acyl and aroyl groups on o-toluidine have on the yield of indazole when prepared by Barclay's method was studied.

3. A mechanism for the reaction has been suggested.
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