

Experiments into the alkali hydrolysis of N,N-diethyl-toluamide (DEET)

By Boffis

Following earlier attempts at acid hydrolysis of so called DEET (N,N-diethyl-3-toluamide), the main active ingredient of most common insect repellent sprays, with 85% sulphuric acid (sulphuric acid mono-hydrate) that resulted in a dark brown intractable oil I decided to try a series of experiments using alkali hydroxides. This was based on several claims or comments by SM members in the following thread <http://www.sciencemadness.org/talk/viewthread.php?tid=11081#pid134404> started by mbrown3391. His opening post asks a general question about the possible preparations of diethylamine and then proceeds to list three possible routes. The first of his proposed methods was by the alkali hydrolysis of the DEET which is N,N-diethyl-3-toluamide or N,N,-diethyl-3-methylbenzamide, as you prefer. But in spite of vast amounts of heated argument, most of it of rather poor quality, that ensued no one ever seems to have posted a detailed description of their experiments and results that constitutes a workable procedure. On page 5 of the link above Science Squirrel posts a brief experimental description of his attempts at alkali hydrolysis of the amide and concludes that under the conditions he used hydrolysis was very slow but presented no quantitative data. He boiled the originally alcoholic reaction mixture for an hour without perceptible production of amine vapour so then distilled off the alcohol and refluxed the aqueous mixture for a further hour. This resulted in limited production of diethylamine so Science Squirrel added ethylene glycol and refluxed for another hour. This yielded more abundant diethylamine but he concluded that it would require very long refluxing, perhaps 24 hours or more.

Science Squirrel's work seemed to point to base hydrolysis with ethylene glycol or similar medium as being the way forward. On page 4 of the linked SM thread above Nicodem posted a link to a paper that describes the acid hydrolysis of similar aromatic amides while on the following page he goes on to mention that in a footnote in the paper they state that N,N-dialkylamide are very resistant to acid hydrolysis. This and my own attempts at acid hydrolysis (total failure) convinced me that base hydrolysis was the way to go.

For the alkali hydrolysis experiments a single source of "jungle strength" formulation was used. It claimed to be 95% diethyl-toluamide with an unspecified amount of lime oil and 0.1% pyrimethrines. The lime oil content is probably <1% as a perfume so that leaves about 4% of unknowns; no water soluble component appeared to be present. The experiments described below were carried out on the "as bought" material without any pre-treatment.

Initial experiment:

My initial trial with alkali hydrolysis used 10ml of 95% DEET (roughly 0.05 M) in 20ml of 50% aqueous potassium hydroxide (roughly 0.17 M) and 30ml of ethylene glycol. The mixture was heated in a 150ml conical flask with a magnetic stir-bar on a stirrer hotplate. The flask was fitted with a still head and a Liebig condenser flushed with cold water. A delivery adapter on the end of the condenser just dipped into a beaker containing 20ml of water (Note 1) and a carefully measured amount of hydrochloric acid and a few drops of bromophenol blue indicator. The purpose of this was to allow the monitoring of the reaction; initially 3.5ml of 30% hydrochloric acid were added to the collection water, roughly 0.033M or two thirds of the theoretical requirement. The idea being that when the indicator changed colour the reaction would have reached the two thirds point and further acid could be added and so on. The reaction mixture was heated until it just began to boil very slightly. The reaction mixture did not become homogeneous immediately but emulsified and rapidly darkened to a dark brown colour. In spite of the continuous boiling very little appeared to distil off

but after about 3.5 hours the indicator changed to a blue colour and a further 1ml of 30% hydrochloric acid added. The level of liquid in the receiving beaker slowly rose by about 35ml over 9 hours but the indicator did not change to blue violet again.

After 9 hours the heating was stopped and the reaction mixture cooled to about 35°C and poured into a small separating funnel. It was now a dark brown but still cloudy and on standing separated into a slightly cloudy brown aqueous phase and a small amount of dark brown oil that was discarded. The aqueous phase was separated while still warm and reheated in a beaker with about 1.5g of decolourising charcoal (BDH brand) and vacuum filtered hot. The resulting filtrate was a clear medium brown (tea like) solution; it was acidified with 18ml of 30% hydrochloric and the straw coloured suspension cooled to room temperature. The cold suspension was filtered, the cake washed with 50ml of water and dried to give 5.060g of crude toluic acid which is about 75% of theory.

Attempts were made to recrystallize the product from isopropanol both pure and diluted with water but this fail due to the tendency of the material to separate as an oil on cooling and then solidify. So an attempt was made to purify the acid by recrystallizing the sodium salt. The acid was dissolved in 20ml of water and 3.7ml of dilute (1M) sodium hydroxide solution. The solution was heated to boiling and a little (roughly 0.1g) of decolourising charcoal added. The slurry was filtered while still warm to give an almost colourless filtrate but no crystals formed on cooling. The solution was then evaporated in a shallow basin at about 40°C to a small volume. The residue was rather syrup like and refused to crystallise even after chilling in the fridge and scratching the basin. The acid was re-precipitated by diluting the syrup to 20ml again and adding 4ml of 30% hydrochloric acid. The initial precipitate appeared oily but it soon became a cream coloured solid. The granular, cream solid was filtered off, washed with water and dried to give 4.20g of crude m-toluic acid. The next attempt was to recrystallize the material from boiling water. The whole of the remaining toluic acid was added to 300ml of boiling water and simmered until no more solid dissolved and the undissolved material settled to the bottom as a light brown oil. The oil was allowed to merge into a single globule and the clear supernatant liquid poured into a clean beaker where it proceeded to crystallise as soft white needles, when cold these were filtered off washed with a little cold water and dried to give 2.34g. The brown globule was washed with warm water and dried, it could not be recrystallized from isopropanol so it was dissolved in the minimum of 1M sodium hydroxide solution, diluted to 25ml and treated with charcoal. The almost colourless filtrate was acidified with 30% hydrochloric acid causing the free acid to crystallize as creamy white scaly crystals. These were filtered off, washed with water and dried to give 0.741g of an acid that appeared to be distinct from the m-toluic acid (Note 2).

The aqueous collection liquor was evaporated down in a glass bowl on a hotplate until no more water or HCl escaped and cooled uncovered until the temperature dropped below about 60°C (bowl could just be handled by the base) and then covered until it cooled to room temperature. The very deliquescent, cream coloured, crude diethylamine hydrochloride weighed approximately 4.13g but its weight increased rapidly while weighing and may not have been fully dry when evaporation was stopped but this indicates a recovery of at least 70% or so (note 3).

Note 1: There is a serious tendency to “suck back” so that it is important that the delivery adapter only just reached the aqueous acid. To compensate for the increasing volume of liquid in the beaker as the reaction progresses the beaker was lowered by means of a series of wooden blocks of slightly different heights. Thinner blocks as the liquid height increased. A scissor jack could also be used if available.

Note 2: I have some p-toluic acid and will compare this material with it. There appears to be a relationship between the solubilities of the methylbenzoic acids and the equivalent benzene-

dicarboxylic acids (the phthalic acids); the m-isomer being the most soluble in each case and the p-isomer being the least.

Note 3: In later preparations it was found that it is best to heat the diethylamine hydrochloride until it melts. The glassy crystalline plates that result on cooling are much less prone to atmospheric moisture.

Based on this initial experiment with alkali hydrolysis I decided to try increasing the reaction temperature by reducing the amount of water. To this end solid potassium hydroxide was used and water added until the KOH liquefied in the glycol. About 20ml of water were required for roughly 50g of 85% KOH. Since the yield of diethylamine appeared to reflect the degree of hydrolysis fairly accurately the reaction progress was monitored as before but this time Congo Red paper was used to monitor the acidity of the collection liquor, when the paper no longer turned blue more acid was added from a cylinder containing the theoretical amount of acid.

Experimental details preparatory scale

51g of 85% KOH flakes were placed in a 500ml conical flask equipped with a magnetic stir bar and 135ml of ethylene glycol were added. To this were added 20ml of water and 45ml of 95% "jungle strength" DEET without any pre-treatment.



Figure 1; Left, KOH in ethylene glycol Right; 20ml of water and 45ml of DEET product



Figure 2; all ingredients mixed T=0 and the darkened mixture after 10 minutes heating

The conical flask was fitted with a still head and a small Liebig condenser; on the end of the condenser there was a delivery adapter that just dipped into a beaker containing 35ml of water and 20ml of 30% hydrochloric acid to capture any diethylamine that passes over. Stirring and heating were commenced; initially a pale yellow emulsion formed which rapidly turned dark brown. When the stirring was turned off briefly the mixture separated into two phases. After about 4 hours the mixture became homogenous and slightly less dark.



Figure 3; the general distillation set-up and the mixture becomes homogeneous after 4hrs

After 4½ hours the collection solution became alkaline and the amine began to escape so another 5 ml of 30% hydrochloric acid were added which brings the hydrochloric acid in the collection liquor to slightly more than that theoretically required. The slow distillation was terminated after 10 hours by which time the colour of the reaction mixture had become a clear light brown rather like tea and about 30 ml had distilled over.



Figure 4; the reaction mixture after 10hrs and cloudiness after dilution with 100ml of water

The reaction mixture was cooled to a little above room temperature and the equipment partly dismantled. There was a strong smell of diethylamine to the reaction mixture so 100ml of water were added to the flask and the distillation continued until another 25ml had passed over and entrained in the original collection solution by which time the distillate no longer smelled of amine. The final collection liquor was still fairly acid to Congo Red paper, was cloudy and smelled of limes (from the perfume used in the original product).

The flask contents were cooled a little and then poured into 300ml of cold water to give a slightly cloudy, light brown solution. This was acidified with 100ml of 30% hydrochloric acid, chilled in the fridge to about 5°C and filtered. The pale straw coloured cake was washed with a little cold water and sucked as dry as possible. The cake was dried on a watch-glass at about 35-40°C overnight to yield 29.67g of crude m-toluic acid.

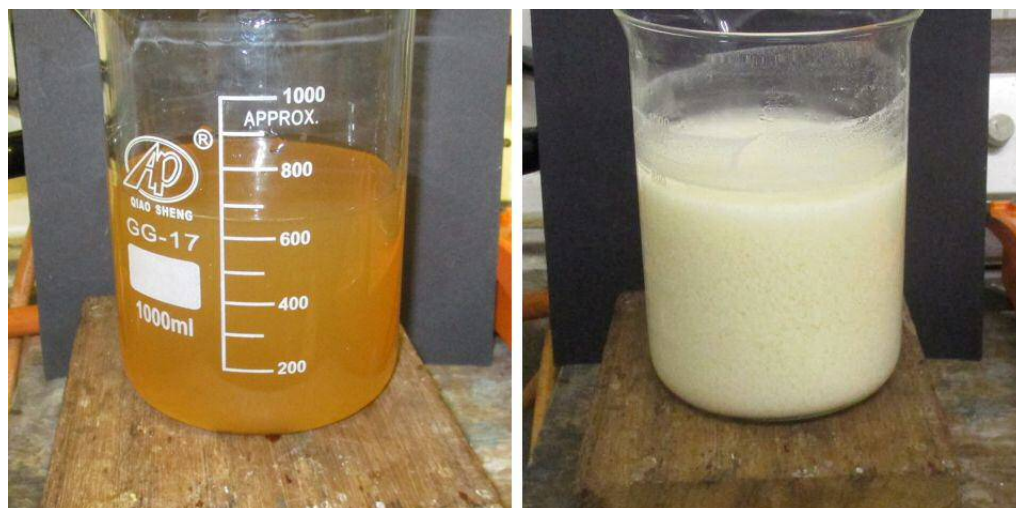


Figure 5; the final reaction mixture diluted with 300ml of water (left) and then acidified (right)

The diethylamine collection liquor was evaporated down slowly in an open flat bottom glass basin with frequent stirring until the liquid completely solidified on the stirrer rod when it was removed from the liquid. Too rapid an evaporation causes the liquid to sputter. As the liquid evaporated the oil disappeared and the mixture solution became transparent. As the final pale straw coloured liquid cooled it was stirred and any lumps broken up until all of the liquid had solidified when it was covered with a watch glass and left to cool. When cold the bread-crumb like solid was transferred as rapidly as possible to a pre-weighed boat and weighed. The yield of crude diethylamine hydrochloride was 23.75g (almost 97% of theory).

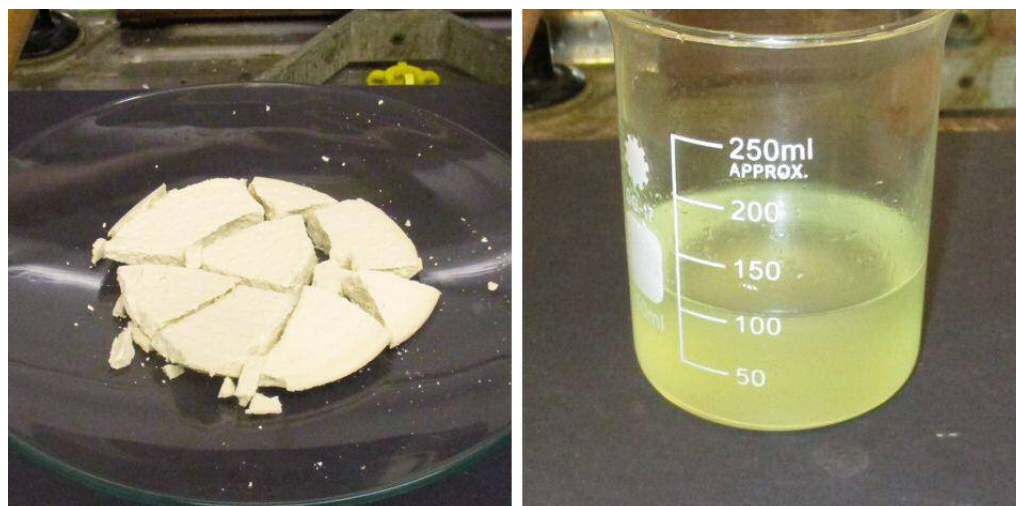


Figure 6; The crude m-toluic acid (left) and the diethylamine collection solution (right)

To purify the crude m-toluic acid it was dissolved in 400ml of water and 24ml of 40% sodium hydroxide solution. The slightly cloudy straw coloured solution was treated with 2.5g of BDH decolourising charcoal and heated for 15 minutes to just simmering and filtered hot. The clear, pale

straw coloured filtrate was acidified while still hot with 30ml of 30% hydrochloric acid and chilled to 4°C in the fridge. The cold cream-coloured suspension was vacuum filtered (9cm Buchner funnel), washed with 200ml of cold water on the filter and sucked as dry as possible. The final air drying was done on a large watch-glass at 35°C to constant weight to give 28.05g of almost white powder of crude m-toluic acid. The yield of dried, crude m-toluic acid was 92.6% of theory.



Figure 7; the collection solution evaporated to about 35ml (note that it has become clear) and the final slightly yellow diethylamine hydrochloride after evaporation to dryness and fusing

Repeat experiment

This experiment was carried out exactly as before to the point where the final reaction mixture, freed of diethylamine, was diluted with 300ml of water. At this point the cloudy solution was treated directly with 2g of decolourising charcoal and filtered before being acidified. The results was a clear light golden brown filtrate that deposited a pale cream coloured crude toluic acid when acidified with 100ml of 30% hydrochloric acid. The yield of dried crude m-toluic acid was 28.88g or 95% of theory.



Figure 8; the fully diluted reaction mixture (left) and the same mixture after heavy charcoal treatment

The crude m-toluic acid was purified as before by dissolving in 400ml water and 24ml of 40% sodium hydroxide and treating with 2g of decolourising charcoal, filtering, washing and acidifying with 30ml

of 30% hydrochloric acid to give a pure white precipitate. The toluic acid was dried on a watch glass to give 27.34g (90.2% of theory) of almost pure white powder.

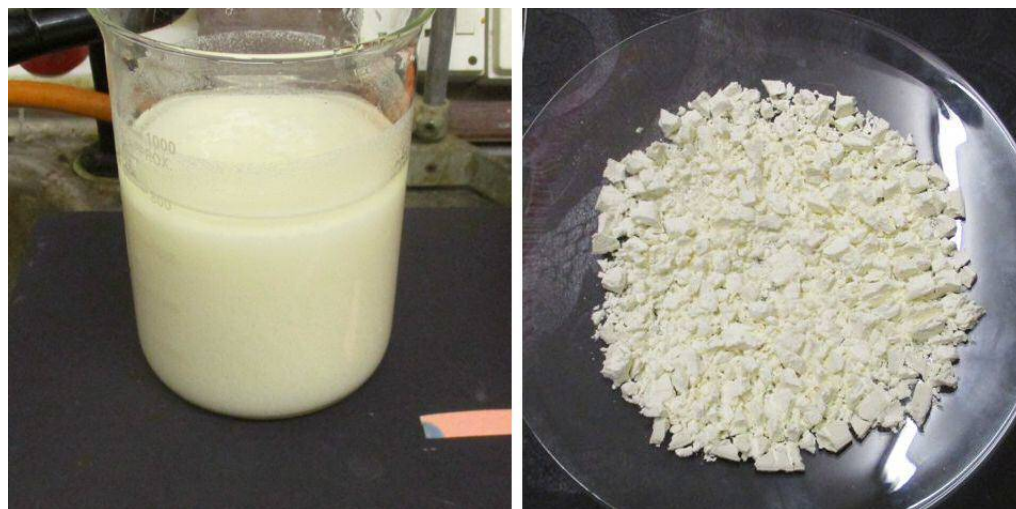


Figure 9; the initial precipitated toluic acid re-dissolved in dilute NaOH, charcoal treated and then acidified and (right), the filtered and dried white m-toluic acid.

Purification of the m-Toluic acid

Some of my earlier investigations of the toluic acid from the small-scale orientation study suggested that the resulting m-toluic acid is not pure and may contain other toluic acid isomers. Attempt to recrystallize the acid from alcohols, with or without water dilution, and water alone failed as the acid separates as an oil and then solidifies but doesn't seem to be any purer than before. The solubility in water is low, 1g failed to dissolve in 50ml of boiling water. Following S.G.Wack's suggestion to use water alone I tried again but this time with larger amounts, I found that about 100ml per gram are required but even then a small amount of brown oil that sinks to the bottom and solidifies on cooling, remains; the clear solution can be simply decanted and allowed to crystallise. With the white acid that has been treated twice with charcoal a little less water can be used but this is not advisable as it tends to start crystallising before any useful manipulation can be carried out on the solution.

Recrystallization as the barium salt

Following several small scale experiments with sodium and barium salts it was found that the latter seemed to be the best option having a reasonable solubility gradient and crystallised well. Initially barium hydroxide solution was tried and while this worked it appears to offer no advantage over barium carbonate which is more accessible and cheaper.

800ml of de-ionised water were placed in a large beaker and heated almost to boiling. 41.85g of crude white m-toluic acid were added to the water followed by 33.03g of barium carbonate powder and the mixture stirred fairly vigorously. There was only a slow effervescence and it took about 10 minutes before the barium carbonate seem to have dissolved but there was still some sticky straw brown scum, inflated by carbon dioxide bubbles, on the surface so a further 8.0g of barium carbonate were added and the mixture simmered for a further 20 minutes by which time only a little straw coloured powder remained undissolved. The solution was dilute slightly to 1200ml, reheated to boiling and filtered hot through a large preheated Buchner funnel. Even so pearly flakes of the barium salt began to crystallise out before filtration was complete. On completion of filtration the solution was poured into a large clean beaker, covered with a watch-glass and reheated to boil to dissolve the salt. The clear faintly tinted solution was allowed to cool slowly to room temperature

(11-12 °C) overnight and then filtered, The crystals were washed with a little deionised water and dried to give 31.27g of pure white pearly plates of barium m-toluate hydrate.

The filtrate was evaporated down to about 500ml on the hotplate and allowed to cool to room temperature again. The crystals were recovered as before to give 15.29g of pearly plates as before. The filtrate was again evaporated down to about 300ml and cooled to yield a further 5.89g of pearly white scales. Further evaporation to about 100ml gave a further 5.96g of fine pearly powder that looked rather less pure and was recrystallized with similar material from earlier batches.

The final filtrate was further fractioned by slow evaporation that is ongoing. It eventually starts to deposit white pompom like aggregates of another phase and it is sometimes necessary to resort to hand sorting of the crystals!

This run gave 52.45g of fairly pure barium m-toluate hydrate as pearly white orthorhombic plates. Loss on heating to constant weight at 120-130° C show that the salt is a dihydrate, so the recovery represents 78% of the theoretical yield of m-toluic acid as its barium salt from this batch but excluding the final crop which was recycled with earlier material.

This run was the last of three experiments into the crystallisation of the barium salt, the total yield from all three attempts was 78.81g of barium m-toluate, which based on 100ml of 95% DEET (my measured density =1.0288) represents a recovery of about 71%. However, further crude m-toluate will be recovered from the final evaporations of the residual filtrates along with the white pompoms of what are believed to be mainly barium o-toluate. Loss of weight at 110-130° C indicates that this salt is a trihydrate and comparison of its morphology with barium p-toluate prepared from laboratory grade (Sigma Aldrich) p-toluic acid, which crystallises in slender glassy prisms, is quite different.

Liberation of the free m-toluic acid

Due to the fairly low solubility of the barium m-toluate and the large volume of solution to accommodate the 78.81g of salt the following procedure was devised to keep the volumes to a maximum of 1 litre. The solution should be acidified hot and allowed to cool as this produces an easy to filter, crystalline product.

The 78.81g was divided into three batches, roughly 30, 25 and 24g respectively (Note 4). The first batch of 30g was dissolved in 1000ml of boil water, stirred until dissolved. When dissolved and a clear solution obtained 10ml of 36% hydrochloric acid (Note 5) were added, the solution stirred and then allowed to cool to room temperature without disturbance. No obvious reaction occurred immediately but on standing the solution quickly turned milky and then, quite suddenly, clear with the separation of white needles of m-toluic acid. When cold the free acid was filtered off, washed with cold water, the washings being discarded, and the next batch of barium salt (25g) was then added to the filtrate. The filtrate was heated to boiling to dissolve the salt and then acidified with 8ml of 36% hydrochloric acid. The solution was allowed to cool as before to room temperature and the second crop of m-toluic acid filtered off using the same filter as before. The filtrate was again recycled for the third batch (circa 24g) of barium salt. This time when the salt had dissolved the solution was made strongly acid to Congo red (about 15ml of 36% HCl) and cooled first to room temperature and then chilled overnight in the fridge to 4° C. The final crop of toluic acid was recovered by filtration as before and washed with copious cold water. The combined crops of m-toluic acid were stirred into 250ml of warm water containing 2-3ml of 36% HCl, stirred for a short while, chilled in the fridge and then filtered and washed with cold water until the wash water failed to reveal barium to sodium rhodizonate/sodium acetate reagent (Note 6). The final product was dried for 12 hours at about 45° C to give 47.97g of pure m-toluic acid (almost 99% recovery).

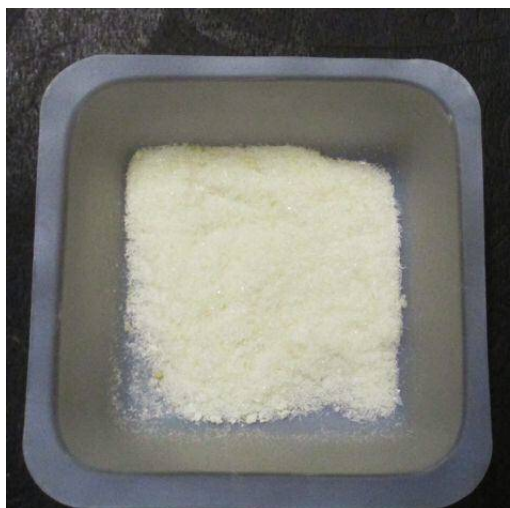


Figure 10; the final product pure m-toluic acid

Recovery of pure Diethylamine from the crude hydrochloride

The roughly 46g of crude diethylamine hydrochloride recovered by evaporation of the amine collections liquor was dissolved in 30ml of warm water and placed in a Quickfit type conical flask equipped with a stir-bar. 50ml of 50% sodium hydroxide solution were added slowly but there was almost no exotherm and no obvious escape of the volatile amine. Any remaining diethylamine hydrochloride rapidly dissolved and then salt started to separate as the liquid itself also separated into two layers. The salt became confined to the cloudy lower, presumably aqueous, layer while the darker brown upper layer was the amine (Note 7). Once all of the alkali had been added a simple still head and condenser were attached and the mixture warmed and stirred on a stirrer hotplate.



Figure 11; the crude diethylamine hydrochloride dissolving in water and (right) the distillation setup

The diethylamine distilled off rapidly between 55 and 59° C as a clear, colourless, mobile liquid. To minimise loss of the volatile amine the receiver adapter was dipped into a small conical flask and the gap around it closed with a loosely fitting piece of tissue. The condenser was flushed with tap water which at this time of year is at about 10-12° C but this proved perfectly adequate to condense the amine vapour even with a tiny Liebig condenser with a 20cm jacket. When the temperature rose about 59° C only a trace of brown scum was left floating on the now almost clear brine solution; this was cooled and discarded.

The yield of diethylamine as a completely colourless liquid was about 42ml weighing 30.67g or about 84% of theory based on 100ml of 95% DEET though the amine may not be completely anhydrous.



Figure 12; (left) the amine rich phase floating on the saline solution and (right) the amine distillate

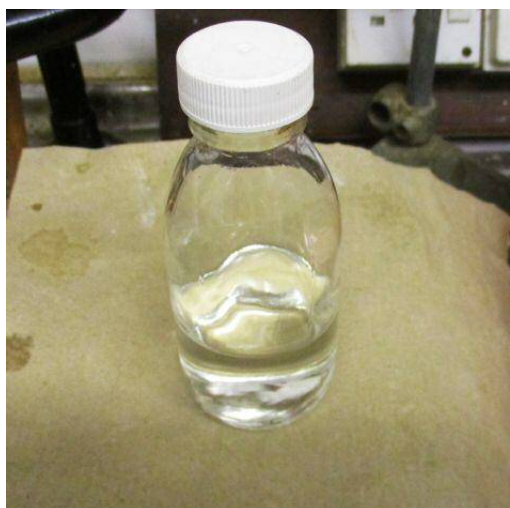


Figure 13; 40ml of fairly pure diethylamine

Note 4; if a more concentrated solution is used the toluic acid separates as a liquid and solidifies into a solid mass that is slightly discoloured. It is probably no less pure but less convenient to handle and requires grinding.

Note 5; for the first two batches, less hydrochloric acid should be used than that required to precipitate all of the toluic acid so that the filtrate for the next batch was neutral. If too much acid is used it cause the immediate precipitation of the free toluic acid when the salt is added to the recycled filtrate, this makes the dissolution of the salt rather slow.

Note 6; this reagent is prepared by adding a 1.5 to 2mm lump of sodium or potassium rhodizonate to 5ml of 3% sodium acetate solution. A drop is placed on filter paper and a drop of the filtrate added a red spot or ring reveals barium is still present.

Note 7; it may be possible with purer diethylamine hydrochloride to simply dissolve the hydrochloride in the sodium hydroxide solution and recover the free amine in a separating funnel. In this case the free amine was too discoloured.

Conclusion

It appears that with care it is quite possible to hydrolyse N,N-diethyl-toluamide (so called DEET) and to recover the constituents in fairly high yield (+70%) as pure compounds by the use of alkaline hydrolysis. Attempts at acid hydrolysis failed to yield any identifiable product but rather caused the formation of much tarry material with 85% sulphuric acid. Given the greater volatility of hydrochloric acid its use as the hydrolytic agent it limits the reaction temperatures and is therefore likely to lengthen reaction times but it may result in fewer by-products than sulphuric acid.

Further work

While I don't intend to carry out further hydrolyses of N,N-diethyl-toluamide I do intend to continue efforts to work up the mixture of barium salts to try and identify the main contaminant in the m-toluic acid. I also intend to try preparing derivatives of the m-toluic acid, possibly through oxidation to isophthalic acid or through nitration which is reported to yield a mixture of two mono-nitro-m-toluic acids.