10. LSD Chemistry

The following has been excerpted from
KOSMOS - A Theory of Psychedelic Experience

The following sections describe what I have found to be the best method for preparing the simple amides of lysergic acid such as LSD, using ergotamine tartrate as the starting material. Over the years I have met a few other “underground chemists” and read books and articles by and about them, and all seem to claim they had found or invented the “best” method for making LSD, while never specifying exactly what it might be! There are also a few “recipe books” available from various sources, and they also do not accurately present the procedures described below nor any alternative ones that work as well. And none even mention the “best” procedure for combining lysergic acid with simple amines (the second part of the preparation). So here I have decided to reveal all, with the conviction that if someone should decide to try to manufacture LSD or similar amides, he might as well have the best information available. The following is not to be taken as an encouragement to do so, and in fact should *dis*courage “amateurs” from even trying. Although I have described the specifics of the procedure in great detail, only those with previous laboratory experience, excellent technique, and university training will be capable of understanding and performing the following with any measure of success, especially with regard to the quality of the product.

Nevertheless, to rebut any objections to my description of these methods, there are really no secrets in the following—all the tricks and specifics of my method can be found in the scientific literature, available in any good university library. The only minor difficulty being to know, from experimentation, which particular tricks work best at each stage of the procedure. Experienced chemists would have little trouble understanding and applying the details described here—many would judge my detailed descriptions as obvious in many cases. Yet amateur untrained persons would not get past many stages in the process. Nevertheless some of the tricks are quite tricky (!) to find in the literature, such as the use of sodium dithionite to protect the ergotamine from decomposition during hydrolysis. I found just a single brief mention of this technique, and was happily surprised at how effective it was.

My requirements for a “good” or “best” method are that it is suitable for use in a small clandestine laboratory, using a minimum of equipment and chemical reagents, especially ones that are difficult to obtain, highly toxic, polluting or dangerous to use or dispose of. Another requirement is that the solvents used should be for the most part reclaimable for further use. Thus, for example, Hofmann's original method for activating lysergic acid by producing lysergic acid chloride hydrochloride using phosphorous trichloride and phosphorous pentachloride, although it works reasonably well, requires bulky equipment (a glove box with a side chamber that can be pumped out to vacuum), excellent ventilation and personal protection, the performance of a tedious sublimation of the PCl5, and leaves one with a nasty mixture of phosphorous compounds in a highly flammable solvent, not easily disposed of and impossible to reclaim for further use. Additionally, due to their possible use for nefarious activities such as the manufacture of explosives, most phosphorous compounds may be difficult to obtain. Several other methods for activating lysergic acid so that it will react with an amine can be found widely in both scientific and amateur literature, but they all suffer from significant drawbacks and do not produce a product that is as easily purified as do the procedures below.

Hydrolysis

The hydrolysis of ergot alkaloids to lysergic acid was first performed by Jacobs and Craig in 1934[1] and is easily accomplished in methanolic solutions of potassium hydroxide (KOH), but the size and purity of the yield of resulting lysergic acid depends critically on the proportions of reagents used, the technique of the separation, the protection of the alkaloids from oxidation and other decomposition, and the reclaiming and conversion of isomeric iso-lysergic acid from by-products of the process.

Procedure[2]

A solution is prepared containing 155 grams KOH, 6 grams of sodium dithionite ($Na_2S_2O_4$), 550 ml H_2O, and 100 ml methanol (MeOH),[3] and added to a 2-litre round bottom standard-taper flask containing 100 grams of ergotamine tartrate. No pretreatment of the alkaloid is necessary. A two-necked distilling head is fitted to the flask with a vertical condenser for refluxing, and permitting the immersion of a sealed tube for the bubbling of nitrogen (N_2) below the surface of the hydrolysis mixture. A glass tube drawn out or fire polished to a small diameter at its tip is best.

The boiling flask is placed in an oil bath maintained at 125 degrees C, and N_2 is bubbled through the mixture, at first vigorously to assist the dispersion and solution of the alkaloid. As the mixture heats and the alkaloid dissolves, the N_2 stream is slowed to 2 or 3 small bubbles per second as measured from a tube leading from the top of the reflux condenser into an open flask of water. Too rapid a stream of nitrogen will bring over too much of the reaction solvent. Ammonia from the decomposition of ergotamine is trapped in this flask, and standardized acid may be used with a suitable indicator to signal the progress of the reaction.

When the mixture begins to reflux, its temperature should be about 92 °C, and refluxing is continued for a further 1 hour. At this point about 95% of the ergotamine has been hydrolyzed, and the reaction is stopped by removing the flask, stoppering it, and cooling it under running water. Continued refluxing does not improve the yield and in fact results in some decomposition, to be avoided. 450 ml of cold MeOH is added to the mixture and the flask and contents are placed in a freezer for several hours or overnight to attain a temperature of minus 15°C or lower.

It is convenient at several points in this and other processes to have a large reserve of thermal ballast at this temperature, and to that end, a 25 to 50 litre open-topped drum of alcohol-water mixture (or antifreeze mixture) should also be kept in the freezer, a large chest type freezer is quite suitable. This drum of cold liquid is convenient for the final cooling of the acidified hydrolysis solution, and as a source of refrigerant for the condenser of a rotary evaporator. This is an essential piece of equipment for later procedures.

Alternatively, one can use a refrigeration compressor and home-built heat exchanger to provide cooling at -15°C. Insulated tubing, a small circulating pump, valves, etc. make up the rest of the apparatus, which in total should be smaller and more portable than a chest freezer.

The hydrolysis mixture, now cooled to minus 15°C, is poured into a 2-litre beaker, preferably of thin stainless steel to facilitate rapid heat transfer, and the beaker placed in

1 Jacobs, W. A.; Craig, L. C., "The Ergot Alkaloids: II. The Degradation of Ergotinine with Alkali. Lysergic Acid," *J. Biol. Chem*., 104 (1934), 547-551. and Jacobs, W. A.; Craig, L. C., "The Ergot Alkaloids: III. On Lysergic Acid," *J. Biol. Chem*., 106 (1934), 393-399.

2 All flasks, condensers, the rotary evaporator et al. are 24/40 standard taper Pyrex laboratory glassware.

3 Readers familiar with the chemical literature will notice that these proportions differ from those in the various classical hydrolysis recipes. This is due to my finding that the hydrolysis is highly temperature-dependent but only slightly dependent on the concentration of KOH. My proportions thus use less methanol, achieving a higher pot temperature, and the total amount of solvent to KOH ratio is more geared toward the next phase of the process, the sulfating of the hydrolysis mixture.

an ice/salt bath to maintain as low a temperature as possible during the acidification process. If dry ice is available, a dry ice/alcohol bath is even better for maintaining a low temperature. A 50% solution of sulfuric acid in water is very slowly added to the dark clear hydrolysis solution, and a thick grey precipitate of mixed potassium and lysergic acid sulfates appears. A robust motorized stirrer with a cage-type impeller is handy for keeping the thick mixture well stirred. The temperature of the mixture is monitored, and not allowed to rise above zero degrees C. The rate of addition of H2SO4 must be adjusted accordingly.

When the mixture attains a pH of 3.0 to 3.5 as measured with pH paper, the addition of H2SO4 is stopped, and the stirring continued until the temperature once again falls to minus 15°C. The mixture must not be acidified below pH3. Congo red indicator paper may be used, it changes to a blue colour at the desired pH range. Just before the acidification is complete, a dramatic thickening of the precipitate will be noticed as the bulk of the lysergic sulfate precipitates out. The beaker and its mixture may be more quickly cooled at this stage by immersion in the drum of coolant in the freezer.

The proper filtering of the precipitates is somewhat slow and tedious but important for a high primary yield of product. The mixture is filtered through a large Büchner funnel by vacuum, a plastic or insulated funnel is best to avoid warming the mixture as it slowly filters. When most of the liquid has run into the flask, the filter cake will be seen to contract and cracks will form allowing air to pass. The filter cake must be continuously and rigorously pressed down with a spatula to avoid this happening, so as to finally produce a hard, practically dry cake of mixed sulfates. This cake, still in the funnel, is then washed with several small batches of pure methanol pre-cooled to minus 15°C, a total of about 200ml may be used. A polyethylene squirt bottle, or a trigger-operated spray bottle is handy for continuously washing the cake using a minimum of solvent. The yellow filtrate in the vacuum flask may precipitate a further small quantity of mixed sulfate, if it is significant it may likewise be filtered off and added to the next step. This is not necessary if only a small amount appears, as the acid filtrate will now be stored in a refrigerator for later recycling.

The washed filter cake is now placed in a large high speed blender/mixer, a spoonful of activated decolorising charcoal is added, and the mixture stirred for several minutes with a solvent prepared from 6% of concentrated ammonia solution in methanol. Enough solvent is added to produce a fairly thin suspension and after further stirring, the mixture is again filtered. The resulting filter cake is washed with a few aliquots of the same solvent and then removed from the funnel, and finally once again treated with 6% ammonia in methanol in the blender, and the combined filtrates are then evaporated in a rotary evaporator. The rotary flask should be a 2-liter round bottom pyrex flask that has been pre-tested at high vacuum, for it is important to evaporate the ammonium lysergate solution until it is a thick paste, and until all traces of ammonia smell have been evaporated off. This requires pumping out the apparatus to quite a low pressure, and one would not want to see the evaporating flask implode! The rotary evaporator (and accompanying vacuum pump as well) must be of top quality, with no leaks and an efficient condenser cooled to well below 0 degrees C by a pump recirculating the coolant stored in the freezer already mentioned (or the compressor/heat exchanger apparatus). A water bath and thermostat adjusted to about 30°C is used to warm the 2l evaporating flask.

A continuous-feed tube into the rotary flask for mixtures to be evaporated is a further refinement, and a bleed needle-valve connected to the nitrogen cylinder/regulator to evaporator vacuum line allows easy control of the vacuum in the apparatus. The admission of nitrogen should also be used to re-pressurize the apparatus after an evaporation is complete. The more one prevents oxygen from mixing with the products being produced, the better will be the quality of the final yield.

The thick paste of crystallized lysergic acid hydrate remaining in the evaporating flask is washed out into a small beaker with portions of cold distilled water containing just a trace

of carbonated water. The resulting slurry is then stirred and cooled in a coolant bath until it just starts to freeze, vacuum filtered, and the cake washed with additional aliquots of ice cold distilled water. The resulting dark clear filtrate is added to the acid filtrate stored in the refrigerator. The nearly white lysergic acid hydrate is then removed to a plate to dry overnight at 30 degrees C. The yield is normally about 30 to 32 grams of d-lysergic acid hydrate containing about 12% water of crystallization.

Treatment of Leftover Filtrates

The leftover solution consisting of the two filtrates from the above process can be stored in the refrigerator for some time, undergoing only slow darkening and decomposition. It contains some of the original sodium dithionite as well as its decomposition product, sulfur dioxide, both of which as antioxidants slow the decomposition of the remaining lysergic and isolysergic acid still in the acid filtrate. There is also a little unreacted ergotamine remaining in this solution. The following process first quantitatively extracts all the remaining alkaloid (mostly iso-lysergic acid) and then converts it to a further acidified solution of d-lysergic acid sulfate using the same process as for the hydrolysis described above. Since the remaining alkaloid in the acid filtrate amounts to about 20% of the total theoretical yield, it is advantageous to save the leftover acid filtrate solutions from 2 to 4 hydrolysis runs before extracting using the following process.

A one-pound bottle of a strong-acid ion exchange resin is converted to its acid form. A resin such as Amberlite IRA-120 in bead form, or an equivalent Dowex resin is suitable. Finely powdered resins have too slow a flow-rate, so the bead form is preferable. It is normally supplied in its sodium form and must be treated with several batches of 2N reagent-grade hydrochloric acid to convert it to acid form. This can be accomplished by first stirring the resin with the 2N HCl in a large beaker, filtering it, washing it with well distilled and de-ionized water to remove sodium ions, and then re-treating the resin with another batch of HCl. The process is repeated four times.

A slurry of the prepared resin in distilled water is poured into a chromatography tube of 60mm in diameter, and filled to about 60cm in length. Distilled water is drained through the column and the top of the resin layer may be protected from disturbance with a filter paper held in place by a heavy stainless steel or porcelain perforated plate. The previously stored acid filtrate solution is adjusted to pH3 to 3.5 if necessary and then slowly siphoned into the chromatography tube, being careful not to disturb the top surface of the ion-exchange resin, or let it run dry and thus admit air to the resin. The flow rate is controlled with a stopcock at the bottom of the tube. If the chromatography tube is poorly loaded or settles unevenly, or the top surface of the resin disturbed by introduction of solvent, the flow is likely to become uneven and maximum absorption and separation not achieved. The flow rate of the acid filtrate is adjusted to about 2 drops per second. Faster flow rates will not allow the alkaloids to be absorbed completely by the resin, and they will leak out the bottom well before saturation of the resin has occurred. Several hours are required to absorb the acid filtrate. A chromatography tube of this size will normally absorb the alkaloids contained in the leftover solutions from 3 hydrolysis runs, i.e., from the hydrolysis of 300gms of ergotamine tartrate.

The progress of the absorption may be followed using a long-wave blacklight, the fluorescing lysergic acid alkaloids being discerned moving slowly down the column as the resin is progressively saturated. The resin itself fluoresces a dull green, whereas lysergic acid alkaloids fluoresce blue-white. The long-wave blacklight is an essential tool in all procedures with lysergic acid alkaloids, even small traces fluoresce intensely, especially if they are in salt form and dissolved in water or alcohol. In the darkened laboratory, the blacklight assists in finding and cleaning up all traces and spills of these pharmacologically very active products. Absorption of toxic ergotamine or lysergic acid itself through skin abrasions or by accidental transfer to the mouth is to be rigorously avoided.

When the blue-white fluorescing zone has advanced to within a few centimeters of the

tube outlet, application of acid filtrate to the top of the tube is stopped, and distilled water is washed through the tube. This washing may be done at increased flow rates. The washing is continued exhaustively for several hours until the eluent has only traces of sulfur dioxide odor. The eluate passing through as the acid filtrate is being absorbed will contain copious amounts of SO2 and the process is best carried out in a fume hood with efficient exhaust fan. A liter of methanol is then passed slowly through the column, after which the alkaloids are then stripped from the column by elution with 7 percent concentrated ammonia in methanol. The methanolic eluate is concentrated to a small volume under reduced pressure in a rotary evaporator, and the resulting solution re-treated with methanolic KOH by the same method as the original alkaloid was hydrolyzed, and in the same proportions. This treatment with KOH hydrolyzes any remaining ergotamine but more importantly converts the iso-lysergic acid produced in the hydrolysis back into its d- (active) form. In solution, all lysergic acid compounds naturally equilibrate to a mixture of the d- and iso forms. In the case of lysergic acid itself, the equilibrium concentration is about 85/15 d-/iso. The re-equilibration of isolysergic acid and re-claiming of leftover products from hydrolysis can result in an overall yield of well over 90% of theoretical. The protective action of sodium dithionate is essential to this overall result.

Since the ion-exchange column method for recuperation of side-products is so effective, one might propose to use it to isolate the original yield, but the acid sulfate method, if a little tedious, works quite well with the quantities described: an ion-exchange column for separating the entire yield of a 100-gram hydrolysis would be much larger and more difficult to control. Also, resins are not nearly as cheap as sulfuric acid, and I haven't had much luck trying to reclaim them after use.

LSD

The first reference I found for the “best” method for LSD preparation was in a book[4] still available occasionally in used condition. In the section by Staab and Rohr we find: (Section 3.2, p72), “Reaction of *N,N'*-Carbonyldiimidazole with Carboxylic Acids to Form Imidazolides.” In a later section, 4.2, we are referred to the original paper[5] that describes the process for the preparation of lysergic acid amides. Those interested to read the originals should be able to find them easily in any good university library, but it is not necessary, since the reaction of lysergic acid with *N,N'*-Carbonyldiimidazole (henceforth CDI) is straightforward and easily accomplished, with just a few caveats.

Firstly, and of utmost importance, is the adherence to strict anhydrous conditions. CDI reacts vigorously with water, liberating CO2. If there is any significant amount of water in the reaction solvent, dimethylformamide (henceforth DMF), then the equivalent quantity of CDI will react with it before converting any lysergic acid. So, one must be able to purify DMF to a highly water-free state, and be able to accurately measure trace water concentration in order to know how much water remains. Chemists will know that it is in practice impossible to remove *every trace* of water from a solvent, and DMF is more difficult to dry than other solvents. So one must dry it to the best of the lab's capability, then measure the concentration of the trace of water that remains, and use just enough excess CDI to eliminate it. In this way, one can convert the lysergic acid totally to its imidazolide. To this end, the determination of water by the Karl Fischer method, using electrometric endpoint, is most effective. The chemist must master this analytic procedure before any attempt is made to react lysergic acid with CDI. The determination of trace water in DMF is a little more complicated than for other solvents, since the end-point will drift considerably over a few minutes. A series of determinations using DMF intentionally contaminated with small but precise quantities of water must be performed, to standardize one's technique.

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4 *Newer Methods of Preparative Organic Chemistry, Volume 5,* edited by W. Foerst, Academic Press 1968.

5 A. Cerny and M. Semonsky, *Coll. Czechoslov. Chem. Commun.* 27, 1585 (1962)

As for the drying of DMF, this too is not as straightforward as one might hope. DMF is very much like water in certain respects, and even at its boiling point, 153°C, far above the boiling point of water, the DMF remains quite reluctant to give up its content of water. Since one will be reclaiming DMF after the reaction to be described below, there will always be some water in it, and drying agents will not do the trick. The reclaimed DMF will also have some benzene in it, for reasons to be described below, and this turns out to be very convenient, for distilling DMF containing 10-15 percent of benzene turns out to be the best drying method! As the DMF distillation pot is heated above the boiling point of benzene, 80°C, one will notice that the distillate in the condenser has droplets of water suspended in the immiscible benzene. Benzene and water form an *azeotrope,* and even without knowing the least thing about this thermodynamic magic, one may use it to advantage!

Even after the benzene has pushed over all apparent water, however, traces still remain in the distillation pot. The DMF may be dried further by continuing the distillation up to DMF's boiling point, changing the condenser that would now still have water adhering to it from the passage of the condensed azeotrope, and continuing the distillation until one has distilled about half the contents of the pot. DMF coming over after that will be about as dry as one can achieve. Again, the use of nitrogen is a good idea: as it is supplied in cylinders, it is essentially totally dry and can be used to fill or flush one's setup, such as the distillation apparatus. Use nitrogen at every opportunity to achieve and maintain anhydrous conditions!

As for CDI, its use has become more and more common since the first descriptions were published, it is an excellent reagent for preparing peptides, proteins, and otherwise difficult to synthesize chemical and biological molecules. It is quite expensive however, another reason to dry one's DMF to the maximum. One of its great advantages is that its only reaction byproducts are CO2 and imidazole, both innocuous for the product one has just synthesized. Compare that to the nasty byproducts resulting from other LSD synthesis methods. CDI is available from various chemical supply houses, but of course it is no secret what it can be used for - so, caution. CDI can, however by synthesized quite easily from imidazole and phosgene[6].

But *phosgene!* you exclaim, where am I to obtain a notorious war-gas and how to handle it? Fortunately, phosgene (carbonyl chloride) is such a useful laboratory reagent that it is widely used and obtainable in small cylinders, or even better, as a 10-15% solution in benzene or toluene, perfect for the CDI synthesis.[7] In the process, it is reacted completely, so no nasty side products remain such as with other LSD preparation methods. Naturally, extremely anhydrous conditions must prevail in this synthesis too: dry the solvents meticulously, heat and pump out the glassware,[8] use nitrogen, etc. And again, use the Karl Fischer determination of water everywhere. The method also provides a very good way for determining the percentage purity of CDI. Since CDI reacts so swiftly with water in the air, just opening the bottle will produce a little decomposition. And the synthesis method will produce CDI of indeterminate purity according to how well one can perform it. So, one can add precisely weighed amounts of CDI to a solvent that has a pre-determined amount of water it it, then back-titrate the remaining water with Karl Fischer reagent, and calculate the percentage purity of the CDI. 80-95% is a common result, even for “pure” CDI purchased from a supplier.

Lysergic acid as produced by the above method contains approximately 12% by weight of

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6 See https://en.wikipedia.org/wiki/Carbonyldiimidazole and H.A. Staab and K. Wendel (1973). “1,1'-Carbonyldiimidazole”. *Org. Synth.; Coll. Vol.*, 5, p. 201

7 Note that the analogous reagent prepared from imidazole and thionyl chloride is *not* suitable for preparing lysergic acid amides.

8 An apparently dry flask, for example, still has oodles of water adhering to its surface, and the only way to remove (most of) it is by pumping out the flask to high vacuum, heating it moderately, and then refilling the flask with dry nitrogen. Even 3-liter round-bottom standard-taper Pyrex flasks may be so evacuated, but not Erlenmeyer-style flasks which have the annoying habit of imploding!

water of crystallization, and, you guessed it, this water must be removed before reacting it with CDI. 50 grams of lysergic acid hydrate is thus dried under high vacuum in a vacuum-tested 2-liter round-bottom flask immersed in a stirred oil bath at 143°C. 140-141°C is not enough, and 145°C or greater will char the lysergic acid somewhat. Precise automated temperature control is therefore essential. It takes 2-3 hours to dry the lysergic acid, and it is beneficial to remove the flask from the bath every 15-30 minutes and shake the contents a bit, so as to mix the powder and avoid that the same part is always against the flask wall. Use nitrogen to raise the pressure inside the apparatus before this shaking. Caution is required at the beginning of the drying, since at vacuum, water vapor emerging from the powder can "blow" some if it out the flask! So, pump out the flask slowly and watch for the bumping/blowing effect. Slow and/or stop reducing the pressure until the lysergic acid powder "settles down". Use the needle valve bleed mentioned above to control the vacuum, and use nitrogen to refill the apparatus. At the end of the drying period one can add another flask to the setup containing a little P2O5 (phosphorous pentoxide, a very powerful drying agent.) Only a very small layer of P2O5 should be used. The P2O5 flask will be outside, not in the oil bath, of course. It is best if the tube connecting the two flasks is wide bore, the same as a 24/40 standard-taper joint. At this stage of the drying, the apparatus is pumped out to maximum vacuum of the pump. The last traces of water can thus be trapped by the P2O5, the surface of which becomes gummy in the process. Be careful disposing of the remaining P2O5 - it reacts rather violently with water.

The reaction to form lysergic imidazolide is straightforward: A suspension of 50gm dry lysergic acid in 1 liter of anhydrous DMF is stirred with a magnetic stirring bar, at room temperature, and an equimolar amount of CDI[9] is introduced all at once. If the flask is stoppered, the stopper might pop out since the reaction yields CO2 whose pressure will slowly build up in the reaction flask. Remove the stopper from time to time. The escape of CO2 from the solvent is gradual, and indicates the success of the reaction. The suspension of lysergic acid should be fine and homogeneous so that the reaction can proceed rapidly. If there are lumps in the mixture, these will be slow to disperse and react. I have noticed that long reaction times allow considerable isomerization.[10] It appears that lysergic imidazolide has an equilibrium concentration much higher in the inactive iso- form than lysergic acid itself or the simple lysergic acid amides such as LSD (88/12 d-/iso-). The equilibrium of lysergic imidazolide is thankfully not very rapid, so if the lysergic acid is finely dispersed, it will all dissolve in a few minutes, and the amine, such as diethylamine, can be added after 10 minutes, 15 minutes maximum. Once reacted with the amine, no further isomerization occurs.

Introducing dry, finely sieved lysergic acid directly into DMF, however, results in the formation of gummy, difficult to disperse lumps. In order to achieve a fine suspension, the lysergic acid (well-sieved so that it is a fine powder) is first introduced into the reaction flask containing only 150ml of anhydrous benzene. A little more benzene may be added, the desired result being a not-too-thick slurry. The magnetic stirrer can usually achieve this without problems after several minutes. One may stop the stirring for a moment and observe the mixture to check for small lumps not yet broken up. Once the lysergic acid is in fine suspension, the anhydrous DMF may be slowly added, with continued stirring.

A small excess of CDI may be used, perhaps 3%, to ensure that all the lysergic acid will be quickly converted to its imidazolide. Small errors in the determination of CDI purity, trace water in the solvent, etc, can thus be taken into account. Any excess CDI present will react with the amine, however, and produce unwanted side products, so one must not use

9 The CDI must be calibrated for purity with the Karl Fischer procedure mentioned above. A calculated excess of CDI must also be added to eliminate water traces from the DMF/benzene solvent, the concentration of which has also been determined with the Karl Fischer titration.

10 The formation of isolysergic imidazolide might be considered a drawback of the method, but it occurs only to a minor degree if the reaction is performed rapidly, and, similar to the conversion of isolysergic acid back to the d-form described in the hydrolysis section, I will describe below an effective process for converting iso-LSD back to its active form.

more than a small excess of CDI. Immediately before the addition of the amine, therefore, a small amount of water is added to the mixture, just enough to react with the theoretical excess of CDI. Lysergic imidazolide reacts only slowly with water, so as long as one adds the amine immediately after the water, no imidazolide should be affected. The reaction of imidazolide and amine is very rapid, but one may continue stirring the reaction mixture for 30-60 minutes.

Purification

The object of the following procedures is to obtain a slightly beige, nearly white crystalline yield of lysergic acid diethylamide tartrate. There are several phases to the purification, all fairly standard methods, and most professional chemists would probably modify my recommendations according to their previous experience with purifying such compounds.

The final reaction mixture from the above process is a DMF solution of LSD in its free-base form, an equivalent of imidazole by-product, some dissolved CO2, and minor amounts of various impurities and decomposition products. These latter compounds cause the mixture to be dark brown, or even a little reddish. The 4 principal steps to purification are, 1) evaporation to a thick syrup, 2) liquid-liquid extractions, 3) chromatography, and 4) crystallization.

1) The reaction mixture is evaporated to a thick syrupy consistency in the rotary evaporator. Dissolved CO2 from the reaction can cause sudden boiling-over at first, so lower the pressure slowly and cautiously using the bleed needle-valve, all the while observing the rate of condensation of solvent so as not to cause boiling. The benzene will of course evaporate over first, after which the pressure will need to be lowered significantly to get the DMF evaporating. The water bath can be regulated to 35°C.

2) When little or no further evaporation of DMF is possible, the flask is removed and the syrupy residue dissolved in 500ml dichloromethane[11] and introduced into a 2l separatory funnel. The organic (dichloromethane) layer is then washed with a few batches of water containing a trace of ammonia. The raw lysergic acid amide is then extracted into an aqueous solution of tartaric acid, and this layer then washed with several portions of dichloromethane. The extractions can be repeated if it is judged that further purification can be achieved.[12] If a significant amount of difficult-to-break emulsion appears between the extraction layers this might indicate that the reactions have produced excessive decomposition products.

The final aqueous/tartaric acid extract is neutralized with ammonia and the raw amide extracted back into dichloromethane. The solution is totally evaporated, whereupon the raw amide will puff up into a dry foam inside the evaporation flask. Be careful not to suck up any of the product into the evaporator body and condenser.

3) Chromatography. The raw amides are chromatographed over silica gel in a solvent

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11 Chlorinated solvents such as dichloromethane are more closely regulated than in my day, since they contribute strongly to depletion of the ozone layer. I assume they are still available to laboratories since alternatives may not perform equally. Every effort to reclaim dichloromethane must be made to minimize the amounts needed. Dichloromethane is extremely volatile, so large amounts will pass through the rotary evaporator condenser and continue on through the vacuum pump. A cold trap at the exhaust end of the pump should be installed.

12 A convenient and extremely sensitive test to determine whether there are traces of lysergic acid compounds along with the impurities in the extracts (or anywhere else, for that matter) is as follows. A 5% solution of para-dimethylaminobenzaldehyde in methanol is prepared, and stored in a dropper bottle for use. A 2-3ml sample of whatever is needing a test is introduced into a small test tube, and a few drops of the DMAB solution is added. A few drops of concentrated sulfuric acid is then slowly added by dribbling it down the side of the inclined test tube with a small pipette or dropper from a dropper bottle. The H2SO4 will flow down underneath the sample/DMAB layer, and with a little jiggling of the test tube, a dark purple ring will form at the intersection of the two layers, its intensity proportional to the amount of lysergic acid compound present.

mixture of 3:1 acetone:dichloromethane. The process is not so much a chromatography designed for complete separation of the components, but rather a batch purification that first removes the highly colored impurities which remain stuck at the top portion of the column, and then achieves an enrichment of the d-LSD isomer, which flows down the column a little more rapidly than the iso-LSD. As I mentioned previously, the equilibrium between the two isomers is about 88:12, but the small amount of isomerization that accompanies the formation of lysergic imidazolide might produce a raw amide mixture a little richer in iso-LSD.

The silica gel to be used should be intended for chromatography and be quite fine and light in consistency, indicating a very high surface-area to volume ratio. It might be necessary to try a few different “brands” to find the best for this particular use.

The chemist needs to develop a satisfactory and repeatable technique to load a chromatography column so that it will flow correctly. A poorly-loaded column will “leak” the mixture in spikes down the side or center, and not achieve a good result. For ~50gm raw amides a tube of 40-50mm diameter and 40-60cm length should suffice. (Larger diameter tubes are increasingly difficult to load to achieve a uniform flow.) The tube itself should be somewhat longer, so that the silica gel/solvent slurry can be poured into it in one go, and then allowed to slowly settle with only a very slow solvent flow allowed out the bottom stopcock. When the silica gel has apparently settled, the tube should be gently tapped so as to settle the gel to its final length. A filter paper and porcelain or stainless steel circular perforated plate should be carefully placed on the top to prevent the silica gel layer from being disturbed. The column is not allowed to run dry!

The raw amides are dissolved in ~50-100ml of the 3:1 solvent mixture. The resulting solution should not be too viscous or it will not flow onto the column evenly, but not so voluminous so as to prolong the time necessary to absorb it on the column. The solution can be siphoned in gradually, taking care not to disturb the top of the silica gel packing. When all the amide solution has been absorbed on the silioca gel, the elution is continued with the 3:1 solvent. Use a slow flow rate, especially at first, until it can be seen that no spiking is occurring as the amides flow down the tube. Dark colored impurities should be easily absorbed and trapped in the top quarter or third of the column, and a blacklight will assist in showing the progress of the amides. As they emerge at the bottom and are collected, each 100ml is removed and evaporated on the rotary evaporator to monitor the progress of the elution. When 70-80% of the original weight of raw amide has been collected, this d-form-enriched portion is thoroughly evaporated, the flask filled with nitrogen and stored in a refrigerator until one is ready to crystallize this main portion. The column is exhaustively eluted with further 3:1 solvent until very little weight is being removed. This portion will contain mostly the iso-LSD that was produced in the reaction and will be converted as described below.

Crystallization

150ml warm methanol is added to the main portion of the crude amide, in its evaporation flask, and the flask turned on the evaporator. No evaporation is effected, this is simply a convenient method to dissolve the crude amide in the rotating flask, immersed in the evaporator's water-bath at 30-35C. When the amide has dissolved, and equimolar amount of d-tartaric acid is added and the flask rotated again in the water-bath. The tartaric acid dissolves and then crystallization of LSD tartrate normally commences promptly, whereupon the contents of the flask is washed into a beaker with small portions of methanol. The beaker is then placed in the freezer to complete the crystallizing. The beaker may simply be covered with a plastic sheet held in place with a rubber band - no special protective measures are needed.

If crystallization does not begin spontaneously, even after the mixture has been placed in

the freezer, a small amount of cold acetone may be carefully and slowly introduced via a pipette, as a layer on top of the methanol solution. *Do not use diethyl ether* as described in other recipes. There is no need whatever to have ether in the laboratory. Crystallization should then commence between the two layers. The acetone layer may be necessary sometimes, as when crystallizing secondary yields from filtrates, or if the amide solution is not of best purity. It appears that some impurities produced along the way can impede crystallization. A mixture of amides overly-rich in the iso-form may also not easily crystallize.

The crop of crystals may be cold filtered after a few hours residence in the freezer, and washed with a minimum amount of cold methanol. This primary yield can be simply dried in the open air at room temperature, since pure LSD tartrate is quite stable and unaffected by oxygen, except in the very-long term. Crystals of LSD tartrate, stored over several years with no special precaution, will slowly turn dark grey, but the decomposition is nearly all at the surface of the crystals, and quite minor: such darkened crystals, observed while dissolving in a little methanol or ethanol/water, will be seen to readily dissolve, and the resulting solution under the blacklight will show the typical and strong bright blue fluorescence. I have not done any quantitative test, but I would estimate that even very old (10+ years), very dark samples are still 80-95% pure, contrary to what one may have heard about the sensitivity of LSD. In solution, or especially when exposed on blotter paper, gelatin squares, or in poorly made tablets however, decomposition is certainly an important factor. More on this subject presently.

Re-equilibration of iso-LSD

The secondary portion of raw amide eluted from the chromatography tube, presumably stored in a flask in the freezer, and all the various filtrates, washings, clean-up of small spills and whatever, may be combined and re-claimed/re-equilibrated using the following process. All tartrate must first be removed however, so the methanolic filtrate from crystallization and various washings must first be neutralized with ammonia and then extracted back into dichloromethane. The methanol will first be evaporated, then some water with a few % ammonia and dichloromethane added and the layers separated in a separatory funnel. The ammonia/water layer may be extracted with another portion of dichloromethane. The combined dichloromethane extracts can then be added to the flask containing the secondary yield obtained from the chromatography tube.

The dichloromethane having been evaporated, leaving again a syrupy residue that will puff-up under vacuum to achieve removal of all solvent, is then dissolved in methanol, and a spoonful or two of strong-base ion exchange resin is added. The resin must be in the OH^- form, and either the bead or powdered varieties of Dowex or Amberlite are satisfactory. Amberlite IRA-400 is suitable, but must be converted from the as-supplied chloride form to the OH^- form before use. Washing with a few portions of 2N reagent grade carbonate-free sodium hydroxide, in a procedure analogous to the conversion of the strong-acid resin used to re-equilibrate lysergic acid, is the method to use.

Under the influence of base, lysergic acid and its amides attain their equilibrium concentration between d- and iso- forms. Free hydroxyl, such as KOH solution (as in the hydrolysis process), might in this case cause some hydrolysis of the iso-LSD, and would also be more complicated to remove after the re-equilibration. The use of the OH^- form ion exchange resin neatly bypasses these drawbacks. The OH^-, although freely available for causing isomerization, is permanently locked to the ion-exchange resin and can simply be filtered off after the process is complete.

Not only does each lysergic acid compound exhibit a specific equilibrium concentration, 85/15 d-/iso- for lysergic acid and 88/12 for LSD, but the re-equilibration process is also specific to each compound for the time required. Lysergic acid in concentrated KOH re-equilibrates almost instantly. But lysergic acid amides, particularly LSD, require much

more time to arrive at equilibrium.

The flask containing the free amides in methanol and the ion-exchange resin is consequently stirred with a magnetic stirring bar for one week. The resin can then be filtered off, washed with portions of methanol, and the solution evaporated to a thick syrup. One might then proceed directly to crystallization, but it will be observed that some decomposition has taken place since the product has not the light-yellow color of the original portion taken from the chromatography column. To achieve best purity, the chromatography is repeated for this second yield. ...And so on. Depending on the amount of starting material in both the hydrolysis and the imidazolide reaction, one will always have "leftovers" that can be re-treated to obtain further crops of crystals. The repetitive process is limited mostly by one's enthusiasm to produce the most from the least!

Dosing method

The final problem of how to distribute one's product has been solved in a few different ways. Dissolving the final crystal tartrate in (for example) vodka and dropping or absorbing the solution onto "blotter paper" has been popular since it can be done anywhere with a minimum of equipment.[13] But the method is certainly the least desirable for preservation of product purity. As the solution dries on the paper, LSD tartrate does not recrystallize, but forms an oil or gum on the paper fibers and thus loses the protective effect of being in the crystalline form. Blotter paper LSD has a limited shelf life, and can decompose significantly over a period of a few weeks, the rate depending on whether it is exposed to light, heat, humidity and perhaps even city air contaminated with acidic products emanating from factories, power generation, etc. On paper, the product is completely exposed to every whim of the environment. So exposed, significant darkening of the paper dose can be observed over weeks, even days. Coating the paper with an impermeable layer might help, but I haven't heard of it being tried.

The advantages of blotter paper do include, however, inspiring confidence in the product since there are very few drugs - even poisons - that are pharmacologically active at the dose range possible to absorb on a small square of paper. Way back when, there were often rumors that certain LSD products had been "cut" with speed or other products, but a tiny square of paper cannot contain an active dose of most of the proposed contaminants. Whether most consumers were aware of this is another matter. Blotter paper has another advantage: one can easily judge the condition of a blotter paper dose—and even verify that it is indeed LSD—by putting it in a small test tube and adding a few ml water. In a darkened room using a blacklight, the bright blue-white fluorescence[14] (mentioned in other sections of this book) can be observed dissolving off the paper. If the fluorescence is weak, or more yellow than blue, the dose is correspondingly weak and/or decomposed.

Occasionally, gelatin squares (windowpane) or sheets of 100+ doses appeared on the market, but this dosing method also suffers from the fact that the LSD is not crystalline therein, but still in a dissolved state. Much of the dose may, however, be protected from the air since it is inside the gelatin layer.

Well-made tablets certainly are the most desirable dosing method for preserving purity, since the LSD is still in its crystalline form, and most of it locked away from light and air inside the tablet.[15] In Mexico, I had brought along with me some Sandoz ergonovine tablets to use as standards, or comparisons with whatever I might extract or synthesize. As an experiment, I took a couple of tabs up on the roof and exposed them to the direct high-altitude high-UV sunlight for a couple of hours. Naturally, the surface of the tabs became much darkened, but breaking one in half showed that just under the surface, the bright-

13 One enterprising chemist even invented a machine to automatically put 100 dose-calculated drops of LSD onto strips of filter paper - see *High Times* magazine, No. 42, February 1979.

14 The fluorescence is the same as that seen in quinine-containing "tonic water" for mixed drinks.

15 This assumes, of course, that the tablet-making mixture is prepared from crystalline LSD plus the excipient and mixed well, i.e., that the LSD is not first dissolved and "dropped" on a tablet.

blue fluorescence was “as-new”. A tablet-making machine is, of course, not the easiest piece of equipment to come by, and not very portable either. Even the best pharmaceutical-grade tablet-making excipients might be hard to purchase safely.

For convenient and purity-preserving distribution of pure LSD to a few friends or professionals for private “therapeutic” or heuristic use, a 1mg/ml solution in ethanol/water is quite stable over long periods of time, especially if kept in dark-colored dropper bottles in the refrigerator. Naturally, one must calculate the dose contained in one drop, etc.

Chemical Mysteries

Two further chemical enquiries of mine still need some resolution. The first deals with *ergine,* (lysergic acid amide, or lysergamide), and the second with an analogue of LSD that I prepared quite by accident but which I could never identify.

The problem of the psychoactive potency of ergine—or lack of it—has crept into the debate about the *kykeon* of Eleusis as well as the use of the same psychedelic molecule by the Central American shamans (*ololiuqui,* discussed in chapter 3 above). The problem was well covered by Dan Perrine in our paper “Mixing the Kykeon”, mentioned previously. Some researchers, including Albert Hofmann too, were never able to attain a significant psychedelic effect from either ergine or its isomer, isoergine.[16] Some have even proposed that the *ololiuqui* of Central America was probably little more than a placebo. Such a criticism would then have to include the *kykeon* if indeed my theory about its preparation is close to the truth.

But as Jonathan Ott remarked to us when we were writing "Mixing the Kykeon", and wondering how we might support our theory against the placebo crowd, in Central America the Catholic Church's Inquisitors much more frequently wrote about, and were apparently far more concerned about the use of *ololiuqui* than of *Psilocybe* mushrooms,[17] so it is hard to believe that the former had little psychedelic effect. And as my own experiments with *ololiuqui* extracts demonstrated, somehow the active principle of this shamanic drug could indeed be very powerful. And then there are a great many amateur psychonauts who have used and appreciated morning glory seeds over the years, few claiming they had little or no psychedelic effect.[18]

In a presentation at Basel in 2006, and later as the final chapter “Kykeon Chemistry” in an edition of *The Road to Eleusis*[19] I ventured the hypothesis that either ergine or isoergine alone, arriving in the brain, had a far less potent psychedelic effect than *the equilibrium mixture of the two.* Remember the comments above about how all lysergic acid compounds gravitate toward a mixture of their two isomeric forms, differing only in the direction which the amide side chain extends out from the main part of the molecule; And also the comments about the approximate equilibrium concentrations and time constants to establish the equilibrium under different conditions, different for each lysergic acid

16 What is not at all clear from the reports of Hofmann *et al.,* is whether the tested compounds were in their free-base or salt forms, and how the doses were administered, whether by directly-swallowed capsule, injection, etc. At first glance this may seem a trivial matter, but in fact may be the key to clarifying this mystery. See the rest of the argument below.

17 “*Ololiuhqui* was far more prominent as an entheogen here in Mesoamerica than those mushrooms — the mushrooms are mentioned only here and there by a few competent chroniclers; yet almost an entire book was devoted to denouncing mainly the *ololiuhqui* idolatry. The annals of the Inquisition contain many times more *autos de fe* for *ololiuhqui* than for mushrooms.” (Jonathan Ott: personal communication)

18 As for psychonauts using morning glory seeds, I remember one friend insisting he got excellent results by chewing the seeds thoroughly, and this may well be a much better way to ingest them since the re-equilibration of ergine might well occur in saliva, and the equilibrium proportions preserved before swallowing. Most who have tried using seeds find the taste is very bitter and disagreable, so may well have swallowed the seeds before they were adequately chewed. To avoid the taste others have taken powdered seed in capsules or wrapped up in a bit of tissue. In these cases there would be little or no conversion of ergine to equilibrium concentrations.

19 Wasson, Hofmann and Ruck, *The Road to Eleusis – Unveiling the Secret of the Mysteries,* Thirteenth Anniversary Edition, 2008, North Atlantic Books, Berkeley California.

compound.

It was only recently that I discovered a paper that documented some facts about the ergine/isoergine transformation[20] that bear upon my suggestions. The lysergic acid compounds I had dealt with over the years were usually re-equilibrated in basic solution (see the above sections) but Martinkova et al. had found that ergine isomerizes to ergine quite rapidly, *in neutral, pH7 solution.* This finding provided a further clue that may help resolve this question of psychedelic potency.

For the moment let me continue my claim that the equilibrium mixture eregine/isoergine is the active principle at the brain's neuroreceptors when the shaman's *ololiuqui* or the *kykeon* is ingested. The point that the paper resolved was how the mixture in each case was produced. The shaman's recipe, as stated in an early chapter here, was to mix the powdered *ololiuqui* seeds with (presumably neutral, pH7) water, wait for a short time, and filter off the liquid portion which was then used in the curing or ceremony. During the short waiting time, the equilibrium mixture would therefore automatically be produced, even though the seeds themselves originally contain almost entirely the ergine isomer. At Eleusis, the preparation method I suggested would also have allowed ergine to remain for a time in neutral or basic conditions, and thus equilibrate. So in both cases the equilibrium mixture is automatically produced by the method of preparation.

What happens next is that the psychedelic preparation is ingested, and immediately finds itself in a highly acid medium in the stomach. Once these alkaloids are in acid solution, the ring nitrogen at the 6-position takes on a proton to form the salt form of the alkaloid. The molecule therefore carries a positive charge and the re-equilibration reaction that proceeds via enol formation at the 8-position is radically impeded or entirely prevented. Thus whatever mixture, or either isomer alone, arrrives in the stomach, it will become protonated and maintain its ergine-isoergine distribution until absorption, moving through the blood, and arriving at the brain's neuroreceptors. If you ingest ergine alone, (or isoergine), only that isomer alone will arrive in the brain. If you ingest the equilibrium mixture, then both isomers will be bathing your various neuroreceptors simultaneously. It should also be pointed out that it will always be the salt form arriving in the brain, the alkaloids having passed through the highly acid, protonating conditions of the stomach, and also being much more soluble than the free base, non-ionized form.

This scenario is the simplest, most parsimonious hypothesis and so most likely closest to the actual events involved in taking these preparations. We may also conclude that since both *ololiuqui* and the *kykeon* were sufficiently active psychedelic agents, and that the only common element of the two preparations was ergine/isoergine, then suggestions that the psychoactivity of one or the other might be due to additional psychoactive chemicals may be ruled out. It remains only to show *why* the equilibrium mixture should be so much more effective at producing a psychedelic experience. Dr. Dave Nichols has criticised the mixture idea on the basis that his research seems to reveal that isoergine must be completely, or very nearly inactive at the 5HT-2 receptor, and I will take him at his word on this. But what might be happening when *both* ergine and isoergine in equilibrium concentration are intimately hovering around adjoining 5HT-2 receptors? I will have to go out on yet another chancey limb to suggest an answer.

In fact I don't have an answer that I would make a large wager on, but only a hint gleaned from some recent receptor research. To me, what this research strongly suggests is that our knowlege of how drugs, especially mixtures of drugs, interact with receptors is still quite subject to not only new developments but possibly even radical overhaul. This is even more the case when we consider that so much receptor research is now necessarily being done *in vitro,* since studying actual receptors in a living organism has all sorts of impossibilites, doubly so if the organism is a human! Whether *in vitro* findings of a very complex nature can be directly transposed to the actual operation of a human brain is

20 Martinkova et al., "Hydrolysis of lysergamide to lysergic acid by Rhodococcus equi A4", *Journal of Biotechnology* 84 (2000) 63–66.

therefore not to be automatically assumed.

Two recent papers suggest to me that the affinity of a receptor, or group of receptors, is not as specific for given ligands as has sometimes been assumed.[21] [22] These articles are very specialist-oriented, and I certainly don't have the expertise to extrapolate the findings to my present task. But I do think they question the position that the equilibrium mixture hypothesis has no basis, that the co-presence of isoergine at or near neuroreceptors in the very restricted volume of a synapse can have no effect since isoergine alone seems completely inactive.

And what if we could actually watch a single ergine molecule, and detect when it "decided" to convert itself to isoergine and *vice versa*? There is only probability that can predict when it will actually do so, the action of a single molecule cannot be predicted with certainty, it might well "decide" to remain in its currect form forever! So what about a collection of ergine and isoergine molecules in the very restricted volume of a synapse? Do they somehow influence each other's probability of conformation change? Is there some kind of mysterious field effect going on so ergine or isoergine molecules "know" the state of brother and sister molecules nearby, and thus "know" whether they should transform themselves to establish or re-establish equibirium conditions? Might a molecule in the midst of equilibrium therefore "see no need" to transform itself and thus bring the mixture *away* from equilibrium? It has been suggested that the limited psychoactivity of an ergine molecule in a 5HT-2 receptor might be due to its sudden "decision" to convert itself to isoergine, whereupon it no longer fits in the receptor and pops out. But what if it remains in its active state much longer due to this field effect? All of the above is of course silly speculation, unless... On a somehat smaller scale than molecules, physics has noted all sorts of silly behaviors at quantum dimensions. Perhaps in the synapses too.

Second Center of Asymmetry

The 4-ring lysergic acid structure has a center of asymmetry at the 8-position, where the amide side-chain is attached, and which accounts for the d- and -iso frms of lysergic acid compounds. But another center exists that is not much discussed, since there are no drugs that take the form of L-lysergic acid derivatives. The second center of asymmetry is at position 5, where the attached hydrogen normally projects toward the viewpoint usually depicted in diagrams such as in part 2 of "Mixing the Kykeon."

I believe that, quite by accident, I prepared the d-diethylamide of L-lysergic acid. Here's how it happened: Remember that d-lysergic acid resulting from the hydrolysis procedure contains about 12% water in its crystalline structure, and that before reacting it, the lysergic acid hydrate must be dried at high vacuum and 143°C. The drying process always results in some minor charring and discoloration, indicating a little decomposition is taking place. I decided to try drying the lysergic acid hydrate directly from a refluxing DMF solution, using the benzene-water azeotrope effect described previously.

Finely powdered LA hydrate was thus slurried in benzene, then DMF added, similarly to the method for reaction with CDI. A nitrogen bubbler-tube was inserted in the flask, a condenser fitted, and provision made for slowly reducing the pressure in the apparatus. The flask was heated slowly in an oil bath at normal pressure, with nitrogen bubbling in so as to keep the LA hydrate well dispersed and therefore easily subject to dissolving. As the temperature increased, it could be seen that the LA hydrate was indeed dissolving, thus releasing its water of hydration into solution. As the temperature arrived at the point where the benzene-water azeotrope would distil, drops of water and benzene appeared in the condenser, in a quantity indicating that the water of hydration was indeed distilling over. By this time, all of the LA hydrate had dissolved, so it seemed that it was indeed

21 Martí-Solano, Maria et al.: "A Dynamic View of Molecular Switch Behavior at Serotonin Receptors: Implications for Functional Selectivity," October 14, 2014 https://doi.org/10.1371/journal.pone.0109312

22 Kenakin, Terry: "Biased Agonism", *F1000 Biol Rep*. 2009; 1: 87.

possible to dry LA hydrate by this method.

The heating and distilling of the benzene-water azeotrope was contiued until no more water was seen condensing, the totality of the benzene now having distilled as well. The pressure in the apparatus was slowly reduced while continuing to heat the flask, the temperature in the flask rising to perhaps a little over 100°C. I assumed that traces of water would remain in the DMF solution, so continued distilling for a short while. I also assumed that little or no decomposition of the LA, now *anhydrous* in the DMF, would occur as long as I kept the temperature well below the 143°C used for drying *in vacuo*.

The flask was cooled to room temperature, keeping a nitrogen atmosphere above the solution, which was now quite clear with nothing precipitated, and only slightly amber-colored. A reaction with CDI was performed as usually done, and proceeded normally, with CO_2 evolution. The DMF was evaporated and the 3:1 acetone/dichloromethane added in preparation for the chromatograpy step. The crude syrupy LA amide dissolved *but quickly formed a crystalline precipitate, totally out-of-character with the usual result!*

The crystalline precipitate was filtered off, and it quickly became obvious that the product was definitly not the normal d-lysergic acid diethylamide previously produced by this procedure. Its solubility was radically different, almost insoluble in acetone or dichloromethane, thus it could not be chromatographed as usually done. It also seemed impervious to hydrolysis with KOH!

My dissapointment was acute, but almost as an afterthought, I dissolved a little in methanol, added an equivalent of tartaric acid, and lo and behold, the solution fluoresced bright blue-white as normal LSD should. I concluded that the lysergic acid ring structure had not been altered, and prepared myself a 30 microgram dose. A normal-for-the-dose psychedelic experience ensued...

In later years I cornered 2 or 3 heavyweight psychedelic chemists at conferences to see if they could enlighten me, but no. I am quite confident due to the tests I made that the compound was *not* the usually-produced lysergic acid diethylamide, but due to its psychedelic activity at the 30 microgram level, and its normal fluorescence, it could not have been anything drastically different. An analogue with different configuration at poisition-5 of the lysergic acid ring structure seems the most probable conclusion.