Lysergic Acid Diethylamide (LSD) Syntheses

from "Recreational Drugs" by Professor Buzz

Introduction

LSD is, without a doubt, the king of hallucinogens. It is rather difficult to make by total synthesis, but with the right starting materials (lysergic acid, ergotamine) it is as easy to produce as your average THC or amphetamine. I call it the king because of the awesome potency, the usual hallucinogenic dose being about 100 to 400 micrograms orally. The amphetamine DOM (STP), which is 100 times more powerful than mescaline, requires a dose of 5 milligrams. This gives one gram of LSD the potential to contain 4,000 to 10,000 doses. With an average of about 6,000 doses per gram, the street value (based on $5 a hit) of one gram of LSD is $30,000.

LSD Synthesis

As with the rest of this book, I will deal only with the synthetic manufacture of drugs (LSD included). If you want to grow the ergot alkaloids that begin the total synthesis of LSD, then you will have to go to the Merck Index and look up the references to the operation. Michael V. Smith's book, Psychedelic Chemistry, has a section on growing Claviceps purpurea, which yield ergot compounds. This section is very complete and informative, but I think that you should also look up the dangers of growing this fungus before doing it, as it causes a type of gangrene that can kill you (not to mention making your arms and legs fall off) upon contamination of your body. As Mr. Smith's book states, this fungus is very temperamental, hard to obtain, even harder to grow and diffficult to work with. Smith's book gives many references and many formulas that you will not see here, but which are of great interest in the making of all hallucinogens (not just LSD). This does not make my book incomplete. On the contrary, I have given more than enough information to make every major type of drug.

My book is not intended to cut in on Smith's book sales. It is intended to give you information and formulas that Smith's book lacks. Where he gives many different types of formulas, I give only the fast, simple and high yielding formulas. Also, you will not see the same formula in both his and my book, unless it is a general method and not specific. What his book lacks, my book gives (equipment, methods, basic chemistry, a wider variety of types of different classes of drugs, glossary terms, easier to understand wordage, how to buy and make precursors, etc.). What my book lacks, his book gives (more variety of hallucinogenic formulas, cultivation of pot and ergot, tests for activity, etc.). I feel it would be a good idea to buy his book and try some of these harder formulas after learning the basics and practicing some of the formulas from my book, for complete understanding first.

Forgive me for wandering from the subject of LSD synthesis. As this first chapter of formulas is for psychedelics, I felt it necessary to explain the difference of the only other book of this type. If you are sharp, and have carefully read my chapter on buying precursors, you should be able to get lysergic acid from a supplier. Be warned, that the DEA must be informed of the purchase by the supplier, according to laws requiring them to do so. Lysergic acid can be made. Following is the general method to give you a very good idea of the procedure and chemicals involved.

Synthesis of Lysergic Acid

By reacting N-benzoyl-3-(B-carboxyethyl)-dihydroindole (see *JCS, 3158 (1931)* for the preparation of this compound) with thionyl chloride, followed by aluminum chloride gives 1-benzoyl-5-keto-1,2,2a,3,4,5-hexahydrobenzindole. This is then brominated to give the 4-bromo-derivative, which is converted to the ketol-ketone by reacting with methylamine acetone ethylene ketol. This is then hydrolized by acid to yield the diketone and treated with sodium methoxide to convert it to the tetracyclic ketone. Acetylate and reduce this ketone with sodium borohydride to get the alcohol, which is converted to the hydrochloride form, as usual.

The above hydrochloride is treated with thionyl chloride in liquid sulfur dioxide, to produce an amorphous chloride hydro chloride, which is converted to the nitrile with sodium cyanide in liquid

hydrogen cyanide. Methanolysis then gives the ester of the nitrile. Alkaline hydrolysis of this last compound, followed by catalytic dehydrogenation in water using a deactivated Raney Nickle catalyst (see JOC. 13, 455 1948) gives dl-lysergic acid.

Total Synthesis Of Lysergic Acid

This is the easiest way to totally synthesize lysergic acid. There are other ways, but after reviewing other methods, I found this to be superior. It is quite complicated and it takes good modern equipment.

JACS, 78, 3087 (1956). 3-Indolepropionic acid, 94.5 g (0.5 mole) is dissolved in 600 ml of water containing 20 g of NaOH. The solution is mixed with 100 g of Raney Nickle catalyst and hydrogenated at room temp in a steel bomb at about 3,500 psi until the uptake of hydrogen stops (about 20-30 hours). Filter off the catalyst and wash it with a little water to remove the product that is clinging to it. Add 85 ml of concd HCl acid to the filtrate, and cool. If your reduction is incomplete, you will now have unreacted starting material separate, and this must be removed by filtration. Benzoylate the filtrate (the Schotten and Baumann method is preferable), using 210 ml of 12 N NaOH 180 ml of benzoyl chloride. Keep the solution alkaline throughout the benzoylation, and keep the temp below 40°C by cooling. When the benzoyl chloride is fully reacted, the reaction mixture is cooled and acidified with 300 ml of HCl acid. Filter the crude product by filtration, wash with water, and extract with four 1 liter portions of hot water. Separate, and crystallize the resulting syrupy product from a few volumes of methanol. Filter and wash with a little cold methanol to get a little over 100 g that melts at 151-153°. This is l-Benzoyl-3-beta-carboxyethyl-2,3-dihydroindole. This can be purchased to eliminate this step.

1-Benzoyl-5-keto-1,2,2a,3,4,5,-hexahydrobenzindole. 118 g of the above product (1-benzoyl-3-B-carboxyethyl-2,3-dihydroindole) is mixed with 200 ml of pure thionyl chloride. This solution is allowed to stand for 30 min, then it is warmed gently for 15-21 min on a steam bath. Excess thionyl chloride is completely evaporated with the temp maintained between 22-26°C in vacuo. The crude acid chloride is dissolved in dry carbon disulfate. This solution is added, in a thin stream, to a well stirred suspension of 240 g of aluminum chloride in 1750 ml of carbon disulfate in a 5,000 cc flask. Note: this must be done under a fume hood. A complex will separate and bog down the stirring device. Heat this mixture under reflux with stirring for 1 hour. Decompose this mixture by adding 500 g of ice, 250 ml of concd HCl acid, and 500 ml of water, all while good stirring is continued. Cooling of this operation is affected by periodic distillation of the carbon disulfate in vacuo. After the decomposition is complete, any remaining carbon disulfate is removed completely in vacuo, and the product is extracted with 2 liters of benzene. The extract is washed well with 500 ml of 2 N NaOH in three portions, and then with water. Dry (with the usual magnesium sulfate), and evaporate to a small volume in vacuo. Add this small volume to several portions of ether to get the ketone to crystallize (add slowly), and filter, then wash with ether to get 85 g of pure title product, mp: 146-147°C.

1-Benzoyl-4-bromo-5-keto-1,2,2a,3,4,5-hexahydrobenzindole. A solution of the above indole (305 g) in 2,200 ml of glacial acetic acid is warmed to 40°C. While the reaction is illuminated with a 250 watt bulb, 352 g of pyridine hydrobromide perbromide is added in portions, over 5 min with shaking. The solution is then heated to 60° and is held between there and 55°C for 30 min. Treat the mixture with carbon, and evaporate to a small volume in vacuo. The residue is taken up with 2,200 ml of chloroform, and wash this solution with several portions of water, dry as above, and concentrate in vacuo. Crystallize the residue from 2,200 ml of 50% acetic acid and 50% ether to get 270 g of title product that melts at 180.5-181.5°C. Another crop can be obtained from concentrating the fltrates. Yield: 30 g of less pure product.

1-Benzoyl-2,2a,3,4-tetrahydro-4-methyl-2-methyl-1,3-dioxolan-2-yl-methyl-aminobenzindol-5-(1H)one. A solution of the last indole product above (270 g) and 307 g of methylaminoacetone ethylene ketol in 4,500 ml of dry benzene is refluxed for 21 hours under a slow stream of nitrogen. The mixture is cooled and 151 g of methylaminoacetone ethylene ketol hydrobromide is filtered off. The filtrate is washed with ice water, then extracted with 2.5 liters of cold dilute HCl acid containing 150 ml of the concd acid. The acid extracts are immediately added to an excess of ice cold dilute NaOH. Extract with 1 1iter of chloroform, dry over magnesium sulfate, treat with carbon and concentrate by evaporation in vacuo. The residual ketol-ketone is crystallized from acetone to yield 220 g, mp: 135-136°C.

5-Keto-4-N-methyl-N-acetonylamino-1,2,2a,3,4,5-hexahydrobenzindole. 20 g of the above product is dissolved in a mixture of 250 ml of concd HCl acid and 250 ml of water, and the solution is kept under nitrogen for 5 days at 37°. Cool the mixture, treat with carbon, filter, and concentrate the filtrate in vacuo to a small volume. Treat the residue with an excess of sodium bicarbonate, extract with cold chloroform, and remove the chloroform by evaporation in vacuo at room temp. The crude diketone is powdered, slurried with 75 ml of benzene-ether, and filtered. Yield: 9.8 g, mp: 105-107°C.

9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-(4,3)isoquinoline. 25 g of the above product is mixed with 550 ml of absolute ethanol. Stir this mixture under nitrogen and cool to -15° with an external freezing mixture. Sodium methoxide is added (17 g) and the mixture is stirred for 10 min at -10 to -12°. Cool to -25°, and the product is filtered and washed (while still in the funnel) with cold ethanol and ether. Without exposure to air the crude ketone is immediately slurried with a little ice water and filtered. Wash with ice water, ethanol, then ether (all cold) to yield 16 g of product melting at 145-147°.

4-Acetyl-9-keto-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-4,3-quinoline. 24 g of the last product is added to 80 ml of cold acetic anhydride. The mixture is held at 25° for about 5 min, then thoroughly cooled, filtered, and the product (a solid) washed with ether to yield 20.5 g, mp: 169-170°. A second crop is obtained by concentrating the mother liquor by evaporation.

A mixture of the last product (1.0 g) and 10 g of palladium carbon (5%), in 35 ml of xylene, is heated under reflux for 4 hours. The catalyst is filtered and extracted with hot methanol and chloroform. The combined extract filtrates and the initial filtrate are combined and evaporated in vacuo. The residue is recrystallized from water to give 0.6 g of a monohydrate product that melts at 255-256°. This product is called 4-acetyl-4,5,5a,6-tetrahydro-9-hydroxy-7-methylindolo-(4,3fg)-quinolinium hydroxide betaine.

4-Acetyl-9-hydroxy-7-methyl-4,5,5a,6,7,8,9,10-octahydroindolo-(4,3fg)-quinoline. 1 g of the above betaine in a mixture of 20 ml of ethanol and 5 ml of water, is treated with 0.08 g of sodium borohydride, and this solution is refluxed for 10 min and kept at 25° for 1 hour after the reflux is finished. The solvent is distilled off, and the residue is taken up in a mixture of chloroform and water. The chloroform solution is separated, dried as above, and then the solvent is distilled off. The residue is recrystallized from a nitromethane-ethyl acetate mixture to yield 0.2 g (21%), mp 193-196°. Not only is this a small scale, but it is a poor yield, requiring you to perform it several times to get enough product to perform the next step. When you have more than enough, convert the product into its hydrochloride form by dissolving in dry methanol and precipitating with dry hydrogen chloride.

4-acetyl-9-chloro-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-(4,3fg)-quinoline hydrochloride. 3.1 g of the above product in its hydrochloride form is dissolved in 75 ml of liquid sulfur dioxide contained in a glass lined, high pressure bomb, or autoclave. Thionyl chloride (1.2 ml) is added and the vessel is sealed and kept at 25° for 6 hours. Vent the vessel carefully and remove the mixture. Evaporate the sulfur dioxide while keeping the volume of the solution constant by the slow addition of dry ether. The amorphous chloro hydrochloride is filtered, washed with ether (dry) and dried by evaporating in vacuo to give 3.5 g of product, mp:130-135°.

4-Acetyl-9-cyano-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-(4,3fg)-quinoline. 40 g of dry, powdered sodium cyanide, is added to ice cold liquid hydrogen cyanide and stirred gently with ice bath cooling. Speed up the stirring, continue the cooling, and add 7.5 g of the amorphous product directly above. Continue stirring for 30 min, then the hydrogen cyanide is distilled under enough reduced pressure to keep it coming over the condenser at a temp below 10-12°. The residue is mixed with chloroform and ice water, and the resulting mixture is filtered. The organic layer of the filtrate is separated and the aqueous layer is extracted with two separate portions of chloroform. The combined extracts (this would include the separated chloroform, as usual) are dried over magnesium sulfate, decolorized, and the solvent removed by distillation in vacuo. Crystallize the product in ethyl acetate. Yield: 3.3 g, mp: 173-174°. Recrystallize again for extra purity.

9-Carbomethoxy-7-methyl-4,5,5a,6,6a,7,8,9-octahydroindolo-(4,3fg)-quinoline. 1 g of the last product is mixed with 15 ml of methanol and 0.25 ml of water. With external (ice bath) cooling add 2 ml of concd sulfuric acid slowly. Seal this solution in a high pressure bomb with a glass liner (or

in a glass tube taking safety precautions in case of explosion) with a nitrogen atmosphere, and heat at 100° for 23-24 hours. Note: I have seen a big pressure cooker (like gramma cans peas with) work for some of these bomb procedures. I do not recommend it, but here is how to do it right, if you feel you must. Use only the great big heavy duty models, in excellent condition, set the pop off (relief valve) for near maximum position; never, ever tamper or modify this valve to get more pressure. Put the product in a glass beaker, put it in the cooker, flush with nitrogen, heat and stay in a different house during the reaction. Carefully turn off heat, notice or record pressure gauge after time has elapsed. Wait until pressure drops noticeably, bleed off remaining pressure and get product.

Treat the mixture with decolorizing carbon and then evaporate in vacuo to 10 ml. Pour onto a mixture of 30 ml of chloroform, ice, and 10 g of sodium bicarbonate. Separate the chloroform layer, and extract the aqueous phase with three 10 ml portions of chloroform. The combined chloroforms are dried, evaporated to dryness in vacuo, and the product is crystallized from benzene to give 1/2 g of product that melts at 159-160°. You may purify more by recrystallizing from ethyl acetate. This is not very much product. As with the procedure 4 steps back, you will have to perform this step over and over. If you try to double or triple the amounts given, you may get more product, but you will hurt the yield.

dl-Lysergic acid. 3.9 g of the last product is mixed with 78 ml of 1.5% potassium hydroxide solution. Reflux for 30 min under nitrogen. 8.5 g of hydrogen sodium arsonate, and Raney Nickle (16 g wet), that has previously been deactivated by boiling in xylene suspension (see JOC, 455 (1948) to deactivate), is added and the mixture is refluxed and stirred under a nitrogen atmosphere for 20 hours. The solution is treated with carbon, and the crude lysergic acid is precipitated by neutralization to pH 5.6, and then filter it off and wash with water. Yield: 1.04 g. A second crop is obtained in the usual manner (0.15 g). Purify by dissolving in dilute ammonium hydroxide, treat with decolorizing carbon, and reprecipitate with carbon dioxide to get a mp of 242-243°. You may be able to get an analytical or laboratory consultant to make one of these products near the final step, thereby eliminating the need to go through all of the steps as described. This will save you much time, but as these people are highly trained, their time will be costly.

Lysergic acid can be made from many ergot derivatives by hydrolysis of these compounds. These compounds include ergonovine, ergotamine, ergokryptine, ergosine, methysergide, ergine, and a few others. Total synthesis of these compounds is impractical, as lysergic acid is made before the alkaloid. You could stop the operation as soon as you reach lysergic acid, otherwise you will have to hydrolyze as described below. There are many analogs of these alkaloids that end with the ine suffix. These are not as suspicious as the former because they lead to an inactive iso-LSD. They will look like this: the ergotamine isomer = ergotaminine, the ergonovine isomer = ergonovinine, etc. These analogs are easily converted to the active forms or they may be used exactly as the non-iso versions to give the iso-LSD, which is converted very easily to LSD as also described below.

Lysergic Acid From Ergot Alkaloids.

Dissolve 20 g of the alkaloid (use any of the above or one of its isomers or a combination) in 200 ml of 1 M methanolic KOH solution (this is made by dissolving 14 g of KOH in 250 ml of dry methanol) in a 1 1iter evaporation flask (heavy walled construction). Evaporate the methanol off. Add 400 ml of 8% aqueous (water) KOH solution to the residue and boil for one hour under a slow stream of nitrogen that is allowed to flow through a small orifice for exhausting purposes. Cool, acidify with dilute sulfuric acid, and shake in a separatory funnel with 1 1iter of dry ether. Separate the lower aqueous layer and filter it with vacuum assist. Wash the precipitate with 20 ml of dilute sulfuric acid. This is lysergic acid; store as described later in this chapter.

There remains a small amount of lysergic acid in the filtrate solution. Remove it by basifying the solution with sodium carbonate, and then bubbling CO2 through it. Filter it off and add it to the other lysergic acid. Now you will need to precipitate the iso-lysergic acid out and convert it. If you did not use any iso-alkaloid then you will have very little iso-lysergic acid, but it is still worth converting. If you used iso-alkaloid, this is a must.

Precipitate the iso-lysergic acid by adding some 10% HNO3, filter, add more portions until no more precipitate forms. Convert it to lysergic acid by adding 3 ml of 10% KOH per every 0.1 g of iso-

lysergic acid, heat on steam bath for 1 hour under a nitrogen atmosphere. Precipitate the changed lysergic acid by acidifying with glacial acetic acid. The total yield of this entire operation (including the iso change) is a little under 10 grams. As stated earlier, you may use only iso-alkaloid in the hydrolysis step above to get iso-lysergic acid which can be used in the synthesis of LSD to get iso-LSD, which can be changed to the active LSD as described later. Note: iso-LSD is not active.

Some sources say that lysergic acid does not need to be purifed. I feel that everything should be purified. In the event that something should go wrong with the formula, you can immediately rule out impurities as the cause. Also, impurities create unwanted byproducts which can be poisonous, creating dangers for the drug user. Purification of lysergic acid is very easy. Dissolve the acid in dilute ammonium hydroxide, treat with decolorizing carbon, reprecipitate (after filtering off and washing product from the carbon) with carbon dioxide.

Convert iso-LSD to LSD. Add 50 ml of ethanol and 5 ml of 4 N KOH per every gram of iso-LSD. Let this mixture stand for 2 hours at room temp. Evaporate in vacuo to get the LSD.

Separate iso-LSD from LSD. Dissolve the residue of the mixture of LSDs from the end of the formula in 120 ml of benzene and 40 ml of chloroform. Add tartaric or maleic acid to precipitate the LSD, filter off, add a little ether and put in refrigerator for several days to get a little more LSD, which is filtered off and added to the rest. Evaporate the filtrate in vacuo to get the iso-LSD and convert as above.

LSD from Lysergic Acid. This is based on the formula taken from CA, 50, 10803d (1956) Dissolve 5.5 g of dry lysergic acid in 125 ml of acetonitrile that has been cooled to -10° and cool further to -20° with an external freezing mixture. Add 8.8 g of trifluoroacetic anhydride in 75 ml of acetonitrile (this solution must be cooled to -20° before the addition). Be careful making this addition, so as not to raise the temp, etc. Let stand at -20° until all the lysergic acid dissolves (about 1/2 hours). Add 7.6 g of diethylamine (or analog) in 150 ml of acetonitrile and allow to set at room temp in darkness for 2 hours. Evaporate in vacuo to get the LSD, which can be separated from the iso-LSD as above.

LSD From Lysergic Acid

This is taken from CA, 57, 5979 (1962). It is designed by Hofmann to give 1-methyl-D-lysergic acid, and is modified to give LSD and iso-LSD. Dissolve 0.54 g of lysergic acid in 10 ml of freshly distilled phosphorous oxychloride, stir 0.42 g of powdered, fresh phosphorous pentachloride. Allow to stand at room temp for 2 min, then at 90° for 2 min, then evaporate in vacuo. Extract the residue with hexane to give lysergic acid chloride hydrochloride. To save time you may extract the reaction mixture without evaporating. Add 2.5 g of the hydrochloride to a cooled solution of 7 ml of diethylamine (or analog) in 25 ml of methylene chloride that is cooled to 0° Note This solution is cooled to 0° before the addition. With stirring add 13.75 ml of dry pyridine and stir for 30 min with cooling to keep the temp at 0° or a little below. Warm to room temp and continue the stirring for 90 min. Evaporate in vacuo to get the LSDs. Separate as already described.

LSD From Lysergic Acid Monohydrate

This is, in my opinion, the best of all the methods. It was designed to be used to experiment with different types of amines, so if you would like to substitute diethylamine with another amine this would be the best bet. It also gives good yields (50% or better) and is very easy. The reference that gives it (JMC, 16, 532 (1973)), also gives potency data for many lysergamides and many of their formulas. The reading is good, interesting, informative, and the method given below gives no useful amount of iso-LSD, so separation of that product is not necessary. Both method A and B were from JMC, 16, 532.

Method A. A slurry of 3.15 g d-lysergic acid monohydrate (monohydrate means dry) and 7.3 g of diethylamine (or 0.1 mole of similar amine) in 150 ml of pure chloroform is heated to reflux. After the lysergic acid is dissolved (a few min) cool the mixture down to where reflux has stopped by removing the heat. Before the mixture cools any further 2 ml of phosphorous oxychloride is added at such a rate as to give reflux (about 2 min). After addition, reflux for 4-5 min further until an amber-colored solution results. Cool to room temp and wash the mixture with 200 ml of 1 M

ammonium hydroxide. The chloroform solution was dried with MgSO4 (this would have to be after separation), filtered, and concentrated by evaporation in vacuo under a temp of 38° (at no time let the temp go over 40°). The last traces of solvent are removed at 2-5 mm. Dissolve the residue in a minimum amount of methanol and acidify with freshly prepared solution of 20% maleic acid in methanol (not aqueous) to precipitate the LSD in its maleate form. Filter the fluffy white needles, wash with cold methanol and air dry to get 2.2 g of LSD that requires no further purification.

Method B. This is proven to be more effective for using substituted amines. Mix the following slurry; 3.15 g of dry d-lysergic acid in 150 ml of chloroform and reflux in a 3 necked flask. As soon as you have the reflux adjusted add 7.3 g of diethylamine (or 0.1 mole of analog) in 25 ml of chloroform and at the same time, from another addition funnel mounted in the opposite neck of the flask, add 2 ml of phosphorous oxychloride so that both the additions begin at the same time. The additions should be timed so that they both finish after 2-3 min. Keep at reflux with gentle heating for another 3-5 min until a clear amber-colored solution results. Cool thesolution to room temp and finish the work up, as in method A directly above, to get 2 g of LSD maleate. As in method A, this method gives very little or no iso-LSD, so don't worry about removing that.

Lysergic Acid Monohydrate

I put this formula in this book specifically for the two methods (A and B) directly above, however, lysergic acid monohydrate can be used on any of the LSD formulas with possible success. I feel this may be easier than the first method given at the beginning of this chapter.

Dissolve 175 g of KOH in 1,750 ml of water in a flask of 5 liters volume equipped with a reflux condenser and a gas inlet tube. If a stirring device is not required, it should be removed and the open neck stoppered. Heat the mixture to 80° under a stream of nitrogen and add 500 g of ergotamine tartrate. Hold the temp at 80° for 2 1/2 hours with bubbling from the nitrogen filled gas inlet tube. Pour the mixture into a 5 gallon polyethylene bucket (made from the same material as a plastic gas can) filled with about 6 liters of ice. Put the bucket in a cooling mixture to cool below 10°. Neutralize the mixture by adding cold dilute sulfuric acid to a congo red end point (pH 4.2). Lysergic acid and potassium sulphate will be seen to precipitate. Let stand for 2-3 hours in the 5-10° cooling mixture. Filter with vacuum assist, and let vacuo suck as dry as possible. Break up the filter cake and put in a 2 liter beaker. Make a solution from 150 ml of liquid ammonia and 2.5 liters of very cold dry denatured ethanol and add to the reaction mixture. Stir for 1 hour and filter. Keep the fltrate and treat the filter cake to 1/2 the ammonia ethanol mixture as above. This second extract is filtered and the cake is washed with 250 ml of the ammoniacal ethanol mixture. Combine the fitrates, and evaporate to total dryness with a strong vacuum and gently heating. Do not heat at too high of a temp. Scrape the product from the vacuum vessel and put into a mortar. Mix 113 ml of methanol with 38 ml of water, and rinse the rest of the residue from the evaporation vessel and dump into the mortar with the rest of the product. The slurry in the mortar is ground up well and filtered. Wash the flter cake with 150 ml of cold water and use vacuum to suck dry for 1 hour. Break up the filter cake and dry at 80-85° under a high vacuum to get about 65-75 g of cream-white to gray-white powder. This is lysergic acid monohydrate.

I think that if you dry the lysergic acid (obtained from the ergot alkaloids by hydrolysis as described earlier) it will also work in methods A and B. This is how you dry lysergic acid: dry under high vacuum at 140-145° for 2-3 hours.

LSD From Ergot Alkaloids

This was invented by Hofmann and is a superior method because you may proceed from the ergot alkaloids to LSD without isolating the lysergic acid. CA, 57, 12568 (1962).

Add 1.2 g of ergotamine hydrochloride to 4 ml of anhydrous hydrazine and heat 1 hour at 90°. Add 20 ml of water and evaporate in vacuo, to get d-iso-lysergic acid hydrazine. 1 g of the lysergic hydrazine is powdered well and added to 40 ml of 0.1 N (ice cold) HC1 acid. To this, cooled to 0°, is added 4 ml of 1 N Na nitrite, with good stirring. Over 2-3 min, add 40 ml of 0.1 N HC1 acid to get pH to 5. Let stand for 5 min, basify with 1 N NaHCO3, extract with 100 ml of ether, and then with 50 ml of ether. Wash the ether layer with water and dry, then evaporate in vacuo at 10°. Dissolve the resulting yellow azide in about 5 ml of diethylamine at 0° and then heat in a metal bomb at 60° for 1 hour. If a bomb is unavailable you may get by with heating for 3-4 hours at 45°

in a vented flask under a nitrogen atmosphere. Also, I would flush the bomb with nitrogen before sealing and heating. Remove heat after time elapses and let stand (after bleeding off pressure for bomb method) for 2 hours and evaporate in vacuo to get 0.7 g of LSD and 0.15 g of iso-LSD. The iso-LSD will not do anything (good or bad) if consumed, so you may leave it in with the LSD. You may also separate it and convert it to LSD as in the formulas ahove.

LSD From Lysergic Acid JOC, 24, 368 (1959)

This is a simple method that gives good yields of LSD with very little (if any) iso-LSD. You will be required to purchase sulfur trioxide from Allied Chemical and Dye Corp (ask for Sulfan B, or SO3), but this is not a suspicious chemical so ordering is not a problem.

Sulfur trioxide-Dimethylformamide complex (SO3-DMF). This is a reagent required for this method of LSD production. A completely dry 22 liter flask (round bottom) in an ice cooling bath is fitted with a condenser, stirring device, addition funnel, then is filled with 10-11 liters of DMF (dimethylformamide) that has been freshly distilled under reduced vacuum. Use drying tubes to protect the reaction from all moisture (including atmospheric moisture). 2 pounds of sulfur trioxide (SO3) are then added, with a great deal of caution, over 4-5 hours with stirring, dropwise. The temp must be held between 0°-5° during this addition. Stir for 1-2 hours after the addition until some separated, crystalline SO3-DMF complex has dissolved. Store in the dark in a suitable vessel, in a refrigerator for not more than 3 months. Upon storage, the complex will turn yellow and then orange. This is normal. As long as it is less than 3-4 months, it is still good. This mixture gives a molarity of 1 (1 M) and can be made using 1/2 or 1/4 of the amounts above to scale down the version, still giving a 1 M solution.

Lysergic Acid Diethylamide. A solution of 7.1 g of lysergic acid monohydrate. As with any of the formulas calling for the monohydrate, you may substitute dry or anhydrous lysergic acid in place of the lysergic acid monohydrate by using a smaller amount of the dry lysergic acid. I have found that dividing the amount of the monohydrate by the constant of 1.1 gives a close amount of dry lysergic to use, e.g., 7.1 divided by 1.1 = 6.5 g, to substitute in the formula. Likewise, the monohydrate can be figured into a formula calling for dry lysergic, 6.5 times 1.1 = 7.1 g. Also, if a formula does not specify if the lysergic acid is to be dry, e.g., add 0.54 g of d-lysergic acid, then always use dry or monohydrate as any water will kill the yield. Dry as stated above. As a general rule dry your lysergic acid as soon as you plan to use it (because it collects H2O from air). 1 g of lithium hydroxide hydrate in 200 ml of methanol is prepared. Distill off the solvent (methanol) on a low temp steam bath under reduced pressure, or evaporate under vacuum. The resulting glass-like lithium lysergate residue, is dissolved in 400 ml dry dimethylformamide (DMF). 200 ml of this DMF is distilled off with 15 mm pressure through a 12 inch helices-packed fractional column. Cool the resulting solution to 0°, and with stirring, quickly add the SO3-DMF solution (50 ml of 1 M). The mixture is stirred with cooling for 10 min and 125.0 mmol. of the desired amine is added (that would be 9.05 g of diethylamine). The stirring and cooling are continued for 10 min after the amine addition, and then the reaction is decomposed by adding 400 ml of water. After stirring thoroughly the reaction mixture is treated with a saturated solution of NaCl. Table salt and water are fine for this if the salt is not iodized. Use 200 ml of the saturated solution on the reaction mixture. Extract the amide (LSD) with repeated portions of ethylene dichloride. Test for completeness of extraction with Van Urk test or hold extract under black light briefly and look for fluorescence as compared with non-extracted ethylene dichloride, or use any indole test. The combined extracts are dried (with MgSO4 as usual), and then evaporated under vacuo to a syrup. Keep the temp below at least room temp. Dissolve the residue in about 60 ml of dry methanol, acidify with solid maleic acid, treat to turbidity with dry ether, and refrigerate for 3-6 hours to get colorless soft needles of LSD maleate which are filtered from the mother liquor. More crystals may be obtained by evaporating the mother liquor in a cool, dark place under vacuum.

Things To Remember When Working With Ergot Alkaloids, Lysergic Acid, And LSD

These compounds are very sensitive and even unstable. This means that the following steps must be taken to keep from ruining your compound or yield.

1. **Always use red or yellow photographic dark room light bulbs during any step of LSD manufacture. Direct sunlight, electric filament, or fluorescent light bulbs (etc.) will hurt the above compounds. Dark room bulbs are cheap and are a must.**

2. Keep all forms of H2O out of the reaction. Thoroughly dry all the glass ware to be used. Use a drying tube filled with anhydrous MgSO4 (calcium chloride reacts with amines in an unfavorable way and should not be used). I can't be there to hold your hand and guide you through every step, so unless the formula says to add water, the drying tube should be in use, and after the water addition is over, the drying tube goes back on. This way the reaction is always protected even if it does not need to be. Better safe than sorry. Also, if you're not sure if you should use dry reagents, use dry reagents anyway. Also dry the lysergic acid (as described above) and any other precursors in whatever drying process required for that compound before use. Dry the finished LSD or even any intermediate along the way after you have completed the product. Likewise, dry an intermediate that you may have purchased from a chemical supplier.

3. Keep oxidizing agents from these items. Even the oxygen in the air can oxidize some of these compounds. The formula states that during some of the reactions above, an inert gas (nitrogen) must be used for an atmosphere inside the reaction vessel. Nitrogen can be obtained in small bottles (tanks) at a very reasonable fee, without any questions asked. Make sure you use a regulator and introduce a slow stream into the vessel by way of a gas inlet tube or an equivalent. Always flush the vessel before putting any reagents into it (flush the air out with nitrogen). I would use a nitrogen atmosphere from the very beginning of the formula to the very end, even if the formula did not specify its use. Very few of the above formulas call for a nitrogen atmosphere during evaporation, but I feel this may be bad for yield and or potency. LSD has many doses per gram, and if you lose 1/2 g because you were too cheap to use three dollars worth of nitrogen, you have lost about 2,000 doses at $5 a dose = $10,000 of LSD wasted. Better safe than sorry? Also, any precursors you make or buy should be stored in a nitrogen atmosphere, as should LSD. This can be done by poking a gas inlet tube into the vessel trust above or a little below the substance) flushing the air out with a moderate stream of nitrogen then quickly reinstall the cap or stopper.
The best way to store LSD is by producing it in the maleate form. This not only makes it resistant to oxidation, but it purifies it, too. Use the procedure above (JOC, 24, 368, or CA, 57, 5979) when you get to the last dry-and-evaporate-in-vacuo step, then treat the residue as specified.

4. **Never subject these compounds to excessive heat, or any type of temperature warmer than the inside of your refrigerator. Even LSD maleate will decompose in excess heat, so store in a refrigerator. Keep evaporation procedures cooled. This will slow the evaporation process down, but that is better than losing the product. Some of the above formulas require heat for a reaction. This is Ok, but do not exceed the temp stated at any time and never heat longer than needed. Also, nitrogen atmospheres are used during heating operation.**

SUBSTITUENTS

LSD analogs (lysergic acid amides) can be prepared by substituting amines in place of diethylamine. The potency usually drops anywhere from 33% to 75% depending on the

substituent. Diethylamine is highly suspicious, and the substituent will produce a lysergamide that is most likely legal, as legislation has only singled out lysergic acid diethylamide. Little work has been done on the potency of substituted Iysergamides, so a little experimentation by you may be in order. Personally, I would like to try substituting a potent phenethylamine or phenylisopropylamine such as DOM (STP) or 4-bromo-2,5-dimethoxyamphetamine. If I could get a government grant, or maybe a grant from a major pharmaceutical corporation, like Upjohn or Lilly, then I could play around with such experiments.

The following substituents give lysergamides with potencies as indicated in doses per gram (remember that LSD gives about 6,000 to 9,000 doses):

Ethylpropylamine	2,000 to 5,000
Morpholide	600 to 2,000
Methylpropylamine	600 to 1,000
Dipropylamine	600 to 1,000
Methylethylamine	400 to 600
Dimethylamine	300 to 400
Pyrrolidide	300 to 400

As a point of reference, DOM (STP) is one of the most powerful amphetamines, at 200 doses per gram. At $5 a line, its value is about 5 times 200 = $1,000 a gram. For more info see JMC, 16, 532 (1973).

Claviceps purpurea is not the only place to get d-lysergic amides. The plant group of Convolvulacea has been found to posses lysergic acid amides such as ergine and several others. These Convolvulacea type of plants do not cause the dreaded St. Anthony's fire, as does claviceps purpurea, and as a matter of fact, they are hallucinogenic if eaten in large doses. Care must be taken that the seeds have not been treated with poison to discourage usage as a mind alterant, or treated with methyl mercury to prevent spoilage.

When these seeds are to be used for LSD syntheses, make sure to clean off the white layer that surrounds them by singeing or mild burning. Also, ask for Hawaiian Rose Wood, as these are the only ones that contain an appreciable amount of lysergic related compounds. These compounds must be extracted as below, hydrolyzed (like ergotamine) as above, and then used in any of the formulas that require d-lysergic acid or possibly used directly in the Hofmann hydrazine method; CA, 57, 12568 (1962). These seeds have very little amide, so you can plan on quite a lot of work in the extraction step. According to A. Hoffer and H. Osmond, the most amide plentiful species (Woodrose) has a minute 3 to 6 mg of amide per every gram of seed. This means that if you extract very thoroughly, you will require a little over 200 g of seeds to get 1 g of amide, which will be reduced further after hydrolysis to give you about 0.5 g of usable d-lysergic acid. Extract as follows.

Pulverize the seeds in a clean blender until they are a fine powder. Put this powder into a beaker, add 1 1iter of petroleum ether to every 900 to 1000g of powdered seeds, stopper the beaker to prevent evaporation and let set for 3 days. Filter off the petroleum ether and let evaporate to make sure no amides were extracted (there should not be much, if any) from the ether. Add 1 1iter of methanol (dry is best) and let soak for 4 days with vigorous shaking, now and then. Filter off the methanol and evaporate it under vacuo (vacuum speeds the process). In the meantime, add 500 ml of fresh methanol to the powder and extract it again for 3 or 4 days.

Filter as before and extract again with about 300 ml of methanol. Combine the residues of all extractions and hydrolyze.