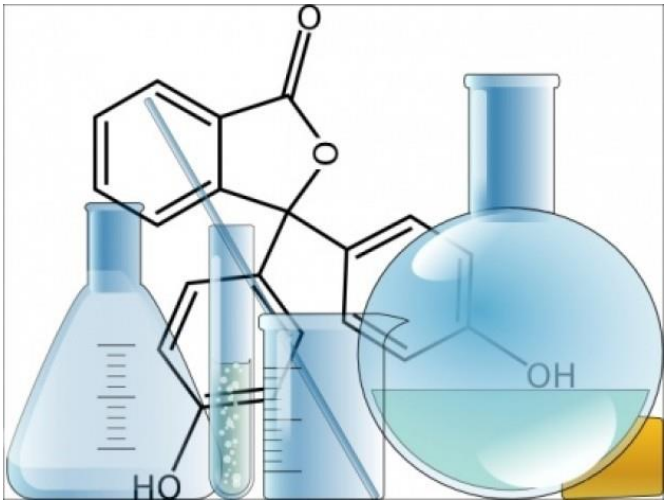
VNIVERSITAT DE VALÈNCIA

DEGREE IN PHARMACY

PHARMACEUTICAL CHEMISTRY

LABORATORY GUIDEBOOK



Laboratory no. 20 - Faculty of Pharmacy (1st floor)

To be allowed to attend the lab practical sessions the student must bring:

This laboratory guidebook **A laboratory notebook (not loose sheets)**

Safety glasses **Protective gloves** **A laboratory coat**

Objectives:

In the Pharmaceutical Chemistry Laboratory Practicals varied experiments about synthesis, isolation and characterization of biologically active compounds will be carried out.
After attending the Pharmaceutical Chemistry Laboratory Practicals the student should be able to:

- Develop lab processes.
- Apply basic techniques of organic synthesis to the preparation of drugs.
- Assess the risks associated with the use of chemicals and laboratory processes.
- Recognize and apply the scientific method.
- Look for and find data related to the subject with a critical outlook.
- Write down the most significant observations on the work carried out and plan the isolation and purification of a substance by proposing a suitable diagram from an experimental procedure.

To reach the above objectives, the students enrolled in this subject will attend six four-hour sessions in which they will carry out four different experiments:

1	Synthesis of diphenylhydantoin
2	Synthesis of benzocaine
3	Synthesis of acetylsalicylic acid
4	Separation of the components of a painkiller tablet

ASSESSMENT:

The mark obtained in the laboratory practicals represents **15%** of the subject's final mark. To pass the course it is necessary that students pass the laboratory practicals. Attendance at the six lab sessions and the introductory seminar is mandatory.
This mark will be based on the development of practical sessions taking into account elements such as the updating of the laboratory notebook, laboratory work, etc. (70%), and qualifying exams: a practical and a written exam on practical issues. This last exam will be administered on the same dates proposed for the exams covering the theory and seminar contents, and a minimum mark of 4.5 out of 10 points is required for the rest of items to count towards the final mark.

LABORATORY SAFETY RULES

The first time you enter the laboratory, please LOOK for emergency exits, safety showers, eyewash fountains, fire blankets and fire extinguishers.

The following rules will be rigorously enforced:

1. Smoking, eating and drinking are FORBIDDEN in the laboratory.
2. Laboratory coat and safety glasses must be worn at all times while in the laboratory. Access to the lab without these safety elements will not be allowed. You must wear protective gloves any time you are working with products.
3. Contact lens wearers run the risk of serious injury to their eyes in the event of a foreign body or chemical contaminating the eye. The use of appropriate safety glasses over prescription glasses is recommended.
4. Liquids must be transferred with the aid of a conical funnel or a pipette. If a pipette has to be used, take the proper rubber bulb. Never do mouth pipetting.
5. Always replace bottle tops as soon as you have finished dispensing reagents and solvents. Avoid inhaling any vapour from liquids or solids. Harmful or odorous chemicals must be handled only in a fume hood.
6. Never handle or pour flammable liquids near heating mantles and hot plates. If you spill a chemical all over any place in the lab, clean it up immediately in the proper manner. If a mercury thermometer breaks up, inform your instructor.
7. Never heat organic solvents directly on a heating source; instead, use a water bath away from the heating source. In those cases, always use Erlenmeyer flasks or tubes, never beakers.
8. Never pour waste chemicals down the sink; always handle them properly and pour them into the proper places. Never put broken glassware in the wastepaper basket. You must give it to the instructor in order to have it replaced.
9. Since electric equipment is used (mantles and plates) both the workplace and your materials must be clean and dry. Equipment must be disconnected and at room temperature before you manipulate any of its elements.
10. Never connect heating mantles, heat or stir plates without a beaker or flask to be heated. Never put the heating control at more than half power.
11. In reflux or distillation setups add the boiling “germ” while the system is still cold. Before heating starts you must verify that the ground-glass joints are tight.
12. Experiments in progress (reactions, distillation, etc.) must NEVER be left unattended!

FAILURE TO FOLLOW THESE RULES MAY RESULT IN A SEVERE REPRIMAND OR EVEN IN YOUR EXPULSION FROM THE LABORATORY

REMEMBER: IN THE LAB…

BE ABLE TO USE ALL THE SAFETY DEVICES

PROTECT YOUR EYES WITH YOUR SAFETY GLASSES

WEAR THE LAB COAT AT ALL TIMES

WASH YOUR HANDS THOROUGHLY

READ THE INSTRUCTIONS CAREFULLY BEFORE DOING THE EXPERIMENT

KEEP YOUR OWN WORK AREA CLEAN AND ORDERLY

MAKE SURE THAT GLASSWARE AND OTHER ITEMS ARE CLEAN AND IN THE RIGHT PLACE

CHECK ALL PIECES TO BE SURE THEY ARE IN PERFECT CONDITION

BE SURE THE SETUPS ARE BUILT CORRECTLY

HANDLE ALL CHEMICALS WITH CARE

USE THE FUME HOOD TO HANDLE VOLATILE CHEMICALS GENERATING HARMFUL OR CORROSIVE VAPOURS

ALWAYS LEAVE MATERIALS CLEAN AND TIDY

WIPE UP SPILLED CHEMICALS IMMEDIATELY

DO NOT EAT, DRINK OR SMOKE

DO NOT SMELL, INHALE OR TASTE ANY CHEMICAL

DO NOT RUN OR PLAY IN THE LAB

DO NOT WORK ALONE

NEVER CARRY OUT NON-AUTHORIZED EXPERIMENTS

IN CASE OF DOUBT ASK YOUR INSTRUCTOR

IN CASE OR EMERGENCY: 112

EMERGENCIES (WORK ACCIDENT)	**UMIVALE**	**963181018**
	UMIVALE PATERNA	**961382675**
	URGENCIAS (24H)	**902365012**

TOXICOLOGICAL INFORMATION (24H) 961382675

PREPARATION PRIOR TO EACH SESSION AND TAKING NOTES IN THE LABORATORY

One important element of your laboratory experience in these practicals consists in learning how to record detailed information about the experiments carried out. Very often, annotations that are not taken in the right manner generate mistakes, frustration and waste of time because of unnecessary redoing of the same experiments previously carried out or due to the lack of clarity in the data collection.

The preparation of the practicals was thoroughly explained in the Organic Chemistry Laboratory Manual (Year 2) but let's recall some aspects:

The laboratory notebook

Never use loose sheets as a laboratory notebook, but use a bound notebook instead (the sheets should not be lost).
All the relevant information has to be included in the lab notebook.
The instructor can ask to review your notebook at any time, so you have to update it every day.
You must never recopy the content of the lab notebook, so write down any remark cleanly and carefully.

In general, the main aspects you should write down in the notebook are the following:

1) GENERAL DESCRIPTION

a) Goal(s).

b) Reaction taking place. Mechanism. Likely side products.

c) Experimental techniques used in the experiment.

d) Required material.

e) Physical properties (melting point, boiling point, density, solubility in water and in organic solvents) and toxicity of reactants and products.

f) Amount of reactants (molecular weight, gr., moles and ratio between them).

g) Special precautions.

2) SEPARATION DIAGRAM

Structural formulas and the likely composition of the different phases should be included.

3) EXPERIMENTAL OBSERVATIONS

4) RESULTS

Related to the final product(s), including structural formula, amount, melting or boiling point, yield, etc.

5) REMARKS TO THE EXPERIMENTAL RESULTS

Items 1 and 2 should be prepared prior to the development of the experimental procedure.
Item 3 should be done while the experimental procedure is in progress.

Items 4 and 5 should necessarily be done once the experimental procedure is finished.

Taking notes at the laboratory

Your notebook must always be near you from the beginning of the session in order to allow you to consult the notes you have prepared prior to the practical session.
At the lab, the notebook is also useful for writing down some data (weights, volumes, physical constants, calculations, etc.). Obviously, it is not possible to prepare this section of the lab notebook beforehand.
The goal is not to transcribe a recipe but to write down the work done and the observations made in a clear and concise manner. These notes should be clear and detailed enough for someone who did not take the notes to repeat the experiment.
Once the product has been purified it is important to write down the relevant data, such as the melting or boiling point, colour, weight and yield.
In the next paragraph the way of calculating the yield is explained.

Determination of yields

The quantitative expression of the efficiency of a particular experimental procedure is given by the yield calculation.
Two different situations must be distinguished:
1) Sometimes the goal of an experimental procedure is the extraction of a compound from a complex mixture with the aim of its purification and identification. In these cases, the yield is expressed as a percentage and is calculated by means of a quotient between the amount of product obtained and that of starting material (usually expressed in weight units), and multiplying this value by 100.
2) Whenever the goal of the experimental procedure is the transformation of some starting products into different final products through a chemical reaction, the reaction yield must be calculated by considering the stoichiometric ratios and the different molecular weights of the products involved.
The theoretical stoichiometry depends on the equation describing the reaction that is taking place. In fact, this *ideal* stoichiometry is rarely observed in the practice because of different reasons. For example, other side reactions giving other products can also occur, or an equilibrium may be reached where an important amount of the starting material remains and can be recovered. Alternatively, a reactant could have been employed in excess or the reaction could be incomplete. All these factors contribute to the fact that the ratios between the reactants used and the ratios observed in the final products do not fit with the ratios described in the theoretical equation.

In a chemical reaction, the theoretical yield corresponds to the number of product moles we can expect to obtain taking into account the theoretical stoichiometry and ignoring the side reactions, reversibility, product loss, etc. Then, the theoretical yield can be calculated from the following equation:

Theoretical yield = (moles of limiting reactant) x (stoichiometric ratio)

The stoichiometric ratio is obtained by dividing the number of product moles by the number of limiting reactant moles considering the stoichiometry of the theoretical reaction. Usually, this ratio has a value of 1 but it is important to pay attention to this expression because in some reactions it is not the case.

Finally, the reaction yield can be easily calculated by dividing the number of moles of the desired product by the theoretical yield, and it is usually expressed as a percentage:

Reaction yield = 100 x (moles of product obtained) / (theoretical yield)

REFERENCES

REVIEWING SOME CONTENTS FROM THE ORGANIC CHEMISTRY LABORATORY MANUAL IS ESSENTIAL AND HIGHLY RECOMMENDED. REVIEW: SAFETY RULES, LABORATORY TECHNIQUES, PREPARATION OF PRACTICAL SESSIONS, ETC.

Additional references:

Medidas de seguridad y higiene en los laboratorios de la Universitat de València. Servei de Prevenció de Riscos Laborals
http://www.uv.es/DSSQA/documentacion/valenciano/PDF/06%20laboratoris.PDF
http://www.uv.es/preven/recursos/preguntes/protocols/decaleg_labs_quim_biol_sp.pdf

Properties of compounds (physical and chemical data, etc.) can be found in the following books or websites:

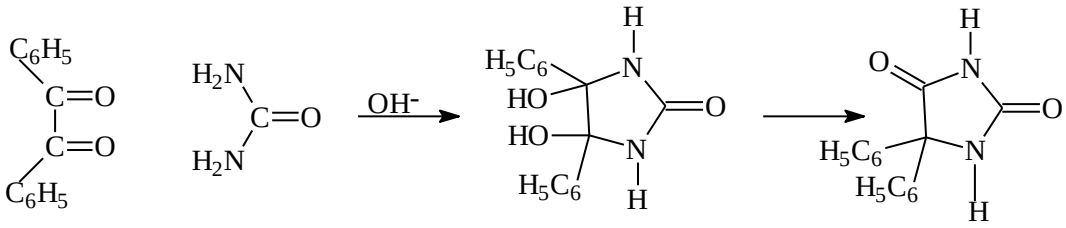
1. ***HANDBOOK OF CHEMISTRY AND PHYSICS***
2. THE MERCK INDEX
3. www.sigma-aldrich.com
4. Instituto Nacional de Seguridad e Higiene en el Trabajo. Fichas internacionales Seguridad Química:
http://www.insht.es/portal/site/Insht/
5. International Labour Organization. **INTERNATIONAL CHEMICAL SAFETY CARDS:**
http://www.ilo.org/safework/info/publications/WCMS_113134/lang--en/index.htm
6. ***STRUCTURE DETERMINATION OF ORGANIC COMPOUNDS*****.** E. Pretsch, P. Bühlmann, C. Affolter, Springer-Verlag (2000)

EXPERIMENTAL TECHNIQUES:

7. ***TÉCNICAS EXPERIMENTALES EN SÍNTESIS ORGÁNICA*****.** Mª A. Martínez Grau, A. G. Csákÿ. Ed. Síntesis (2001)
8. ***QUÍMICA ORGÁNICA EXPERIMENTAL*****.** D.L. Pavia, G.M. Lampman, G.S. Kriz Jr. Ed. Eunibar (1978)
9. ***VOGEL´s TEXTBOOK OF PRACTICAL ORGANIC CHEMISTRY*****.** B.S. Furniss, A.J. Hannaford, P.W.G. Smith, A.R. Tatchell. Ed. Longman (1989)
10. ***CURSO PRÁCTICO DE QUÍMICA ORGÁNICA*****.** R. Brewster, C.A. Vanderwert y W.E. McEwen. Ed. Alhambra (1965)
11. ***JOURNAL OF CHEMICAL EDUCATION***
12. ***EXPERIMENTAL ORGANIC CHEMISTRY: STANDARD AND MICROSCALE*****.** L.H. Harwood, C.J. Moody and J.M. Percy. Oxford: Blackwell Scientific Publications (1999)

EXPERIMENT 1: SYNTHESIS OF DIPHENYLHYDANTOIN

Journal of Chemical Education (1983), 60, page 512 (see ANNEX)



Goals: Synthesizing the anticonvulsant drug diphenylhydantoin. Preparing a heterocyclic system.

Experimental procedure:

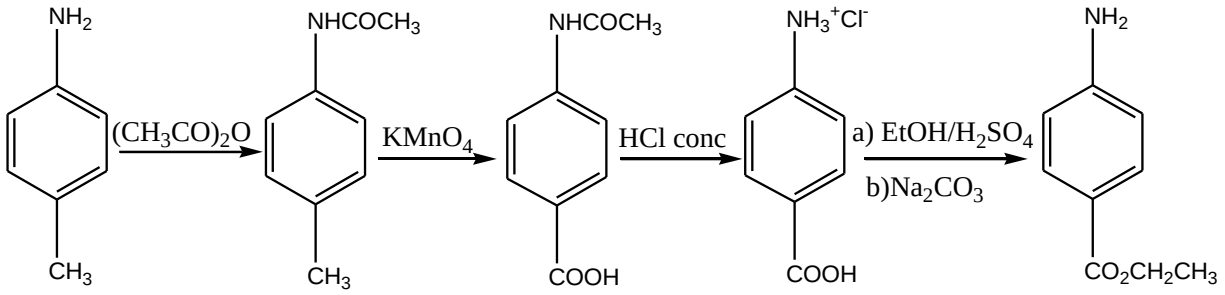
Place 1.3 g of benzil, 0.8 g of urea and 25 mL of ethanol in a 100 mL round-bottom flask. Then, add 5 mL of a 30% NaOH aqueous solution to the above mixture. Incorporate a Teflon adapter and a reflux refrigerant into the flask. Heat the obtained mixture at reflux for 1 h with stirring.

After the heating, cool the reaction mixture and then pour it onto a baker containing water (40 mL). If a suspension is formed filter it by gravity before cooling. Acidify the filtrate with concentrated HCl and observe that a white solid precipitates. Collect this solid by vacuum filtration, dry it, and recrystallize it from ethanol. Once the solid is dry, weigh, calculate the yield and determine the melting point.

Questions

1. What is the correct order in the addition of the reagents to the 100 mL flask before starting the reflux? Why is it important to add ethanol?
2. Why is some water added to the reaction mixture?
3. Why is HCl added at the end?
4. What amount of HCl has to be added?
5. Considering the amounts of benzil and urea used, indicate which is the limiting reactant.
6. In the above experiment, is it possible to obtain 1.7 g of diphenylhydantoin? Why?

EXPERIMENT 2: SYNTHESIS OF BENZOCAINE



Goals: Synthesizing in several steps. Using protective groups in organic synthesis.

Step 1: Synthesis of N-acetyl-*para*-toluidine

Experimental procedure:

Place 2 g of *para*-toluidine into a 100 mL Erlenmeyer flask. Then, in a fume hood, under slow stirring at room temperature, add 5 mL of acetic anhydride with precaution. The reaction is highly exothermic. Allow the reaction mixture to stand for 10 min and then pour this crude into a beaker containing 25 mL of water/ice. If the reaction mixture has crystallized in the flask, drag the solid with a small amount of cold water. Stir the suspension of the product in water with a rod and then collect the resulting solid by vacuum filtration. Once the product is dry calculate the chemical yield. Reserve a small amount of the solid in order to determine its purity by measuring the melting point and by thin layer chromatography. The remaining product will be used as starting material in the next step of the synthesis.

Step 2: Synthesis of *para*-acetamidobenzoic acid

Experimental procedure:

Place the obtained N-acetyl-*para*-toluidine, 100 mL of water and potassium permanganate (1.8 g per gram of N-acetyl-*para*-toluidine) in a beaker. Heat the mixture in a water bath with occasional magnetic stirring until it acquires an intense brown colour (approx. 30 min). Vacuum-filter the resulting hot solution with the aid of a Büchner funnel containing a two-centimetre silica layer on the filter paper (if necessary, put two filters). If the filtered solution has a violet colour, add ethanol dropwise and heat gently until this colour disappears. Once the filtrate is colourless or slightly yellow, allow it to cool, and then acidify with aqueous 20% sulphuric acid. Collect the resulting white solid by vacuum filtration, dry it and weigh it in order to determine the chemical yield. Reserve a small amount of the solid in order to determine its purity by thin layer chromatography. The remaining product is used as starting material in the next step of the synthesis.

Step 3: Synthesis of *para*-aminobenzoic acid hydrochloride

Experimental procedure:

In a round-bottom flask place the *para*-acetamidobenzoic acid obtained in step 2 and add hydrochloric acid (10 mL per gram of solid). Then, assemble the reflux condenser provided with a gas outlet to a trap containing a diluted aqueous NaOH solution. Heat the flask for 30 min. Then, allow the reaction mixture to cool and collect the precipitate of *para*-aminobenzoic acid hydrochloride by vacuum filtration. (WARNING: the product is partially soluble in water; for this reason, the minimum amount of water has to be employed). Allow the obtained solid to dry before weighing and calculating the yield.

Step 4: Synthesis of benzocaine

Experimental procedure:

Mix the *para*-aminobenzoic acid hydrochloride obtained in step 3 and ethanol (10 mL per gram of hydrochloride, minimum 15 mL) in a round-bottom flask and add 0.4-0.5 mL of concentrated sulphuric acid. Heat the resulting mixture at reflux for 2 h. After cooling the mixture, neutralize with a 10% aqueous sodium carbonate solution, before extracting with dichloromethane (3 x 15 mL). Then, dry the organic layers with anhydrous sodium sulphate and evaporate the liquid phase in a rotary evaporator. Recrystallize the solid obtained from ethanol-water. Collect the resulting benzocaine by vacuum filtration and weigh. Finally, determine the melting point and the reaction yield.

** Save small amounts of the products obtained in all the four steps in order to determine their purity by thin layer chromatography (1:1 hexanes:ethyl acetate) and compare them every time with the corresponding starting material.

Questions:

1. There are four steps in the synthesis of benzocaine. Calculate the global yield for a similar synthesis whose partial yields are: 1st step (95%); 2nd step (90%); 3rd step (99%) and 4th step (85%).

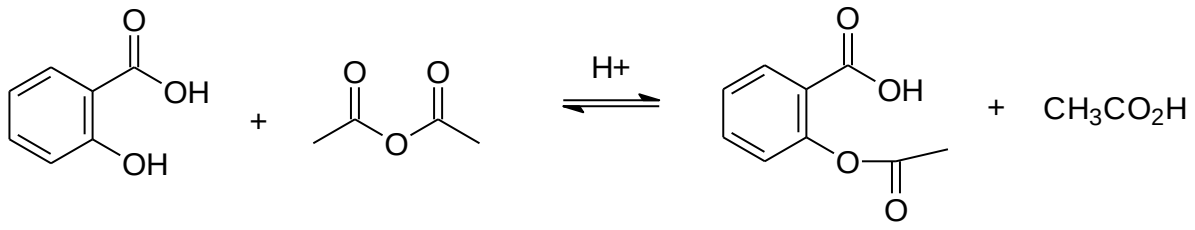
2. Why must the Erlenmeyer flask be dry in the first step? However, the reaction mixture is later poured onto a water/ice mixture. Why?

3. Why is water used as a solvent in the second step? Should we carry out the experiment at this step without stirring?

4. Calculate the yield of the synthesized benzocaine from the amount of *para*-toluidine used in the first step.

5. For step 4 and by means of a flux diagram, indicate the procedures used in the reaction workup and in the purification of products.

EXPERIMENT 3: SYNTHESIS OF ACETYLSALICYLIC ACID (ASPIRIN®)



Salicylic acid Acetylsalicylic acid

Goals: Synthesizing acetylsalicylic acid (Aspirin®). Purifying by crystallization. Determining the purity by means of determining the melting point and with chemical reagents. Performing a chromatographic analysis of the obtained product.

Experimental procedure:
Place, in the following order, 1.5 g of salicylic acid, 3 mL of acetic anhydride and 3-4 drops of sulphuric acid in a 100 mL Erlenmeyer flask. Stir the mixture gently until homogenization and then stir in a water bath at 70-80°C for 15 min. Remove the flask from the bath and pour the warm mixture into a beaker containing 10 mL of water. Stir the reaction mixture for several minutes. Then, cool this reaction crude in an ice bath in order to observe the precipitation of acetylsalicylic acid. Collect the solid by vacuum filtration. At this step, the residual acetic acid, if detected, can be removed from the solid by washing the flask and the solid with small amounts of cold water several times. Save several crystals and keep aside in a clean glass tube.

Crystallization of acetylsalicylic acid in a mixture of solvents:
Transfer the rest of the obtained product into an Erlenmeyer flask and dissolve this solid in the minimum amount of hot ethanol. Add warm water (40°C-50°C) quickly until some turbidity appears, and maintain the heating until boiling. If any impurities are visible, filter the mixture under gravity while maintaining both the suspension and the material hot. Allow the filtrate obtained to cool undisturbed. While the solution is cooling crystals must appear. Cool the mixture in an ice bath to be sure the product crystallizes completely. Finally, collect the acetylsalicylic acid by vacuum filtration and wash the solid in the funnel with a small amount of cold water. After drying, determine the melting point of the solid and calculate the reaction yield.

Phenol assay:
Place a few crystals of the crystallized product into a test tube and add several mL of water. Then, add several drops of a ferric chloride solution and observe the colour.
Carry out the same test with a few impure crystals obtained prior to the purification step, and also with pure salicylic acid.
Compare the colour of these three suspensions.

Chromatographic analysis:
Compare the synthetized aspirin with the starting product by thin layer chromatography (TLC) and determine the R_f.

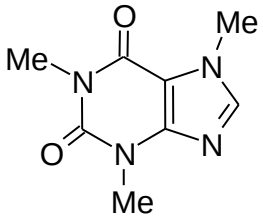
Questions

1. After purifying acetylsalicylic acid through recrystallization in water and analysing the purified product by TLC against standards, besides the acetylsalicylic acid we observe a second product which shows an Rf value similar to the salicylic acid (orto-hydroxybenzoic acid). Why does the purified solid contain salicylic acid if we had previously verified that the starting material had been totally consumed?

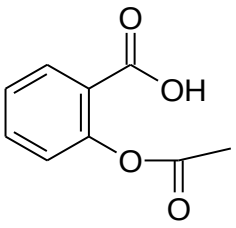
2. What will you find if you determine the melting point of the impure aspirin?

3. Would it be possible to separate aspirin from salicylic acid by means of extracting the mixture solved in an organic solvent with an aqueous NaOH solution?

EXPERIMENT 4: SEPARATION OF THE COMPONENTES OF A PAINKILLER TABLET



Caffeine



Acetylsalicylic acid

Goals: Separating two compounds showing different acid-base properties by means of extraction. Performing a chromatographic analysis of the isolated compounds.

Experimental procedure:
Grind a Cafiaspirin® tablet and mix the resulting powder with the minimum amount of methanol until formation of a suspension. Then, add 20 mL of dichloromethane and extract the resulting solution twice with 15 mL of a 10% Na_2CO_3 aqueous solution to give two solutions, one aqueous (AP1) and one organic (OP).

Dry the organic phase (OP) with anhydrous sodium sulphate, filter under gravity and transfer the filtrated solution into a round-bottom flask. Evaporate the solvents in a rotary evaporator to give a residue of caffeine. (*NOTE: it is advisable that you weigh the clean round-bottom flask before transferring the filtrate so that you can easily calculate the weight of the solid residue by subtraction)*

On the other hand, acidify the aqueous solution (AP1) with HCl and extract with dichloromethane (2 X 15 mL). Dry the organic phases together by means of anhydrous sodium sulphate and filter under gravity transferring the filtrated solution to a weighed round-bottom flask. Evaporate the solvents in a rotary evaporator to give a residue of acetylsalicylic acid. This residue can be purified by crystallization from ethanol/water. Calculate the yield and determine the melting point.

Chromatographic analysis:
Compare the caffeine and the acetylsalicylic acid isolated from the tablet by TLC using a mixture 7:1 ethyl acetate/hexanes as eluent. Determine the R_f of caffeine and acetylsalicylic acid.

OPTIONAL: Extraction of caffeine from Coca Cola®
Experimental procedure:
Place 20 mL of Coca Cola and 10 mL of dichloromethane into a round-bottom flask. Warm the mixture for 2 min and then allow it to cool. Separate the organic phase, dry it with anhydrous sodium sulphate and analyse the solution by TLC comparing it with a sample of the caffeine obtained from the tablet.

Questions

1. Suggest a flux diagram showing the procedure for the separation of the two components of the painkiller tablet.

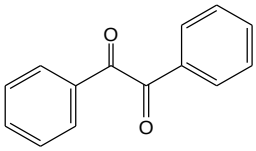
2. In the extraction with 10% Na_2CO_3, what side product could also be formed?

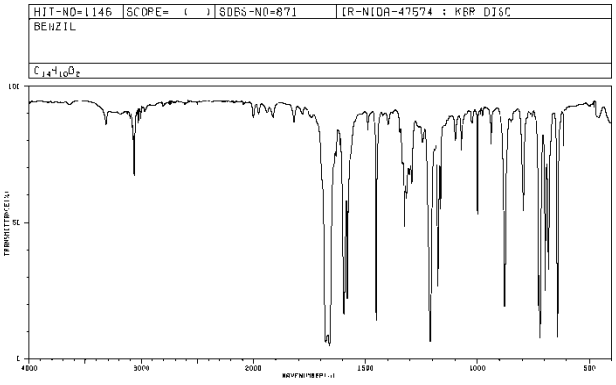
3. Does the calculation of the yield of acetylsalicylic acid performed in the third paragraph have the same meaning as the yield calculated in the previous experiments?

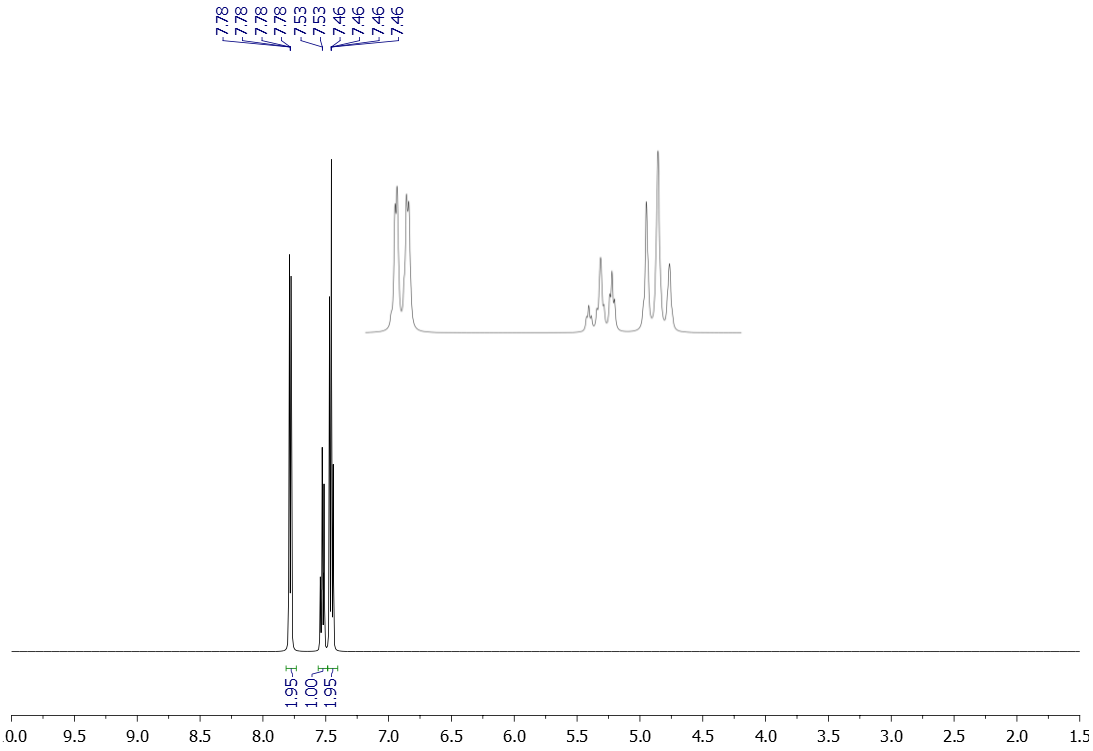
4. Enumerate other analytical procedures that could be used in the characterization of caffeine and acetylsalicylic acid.

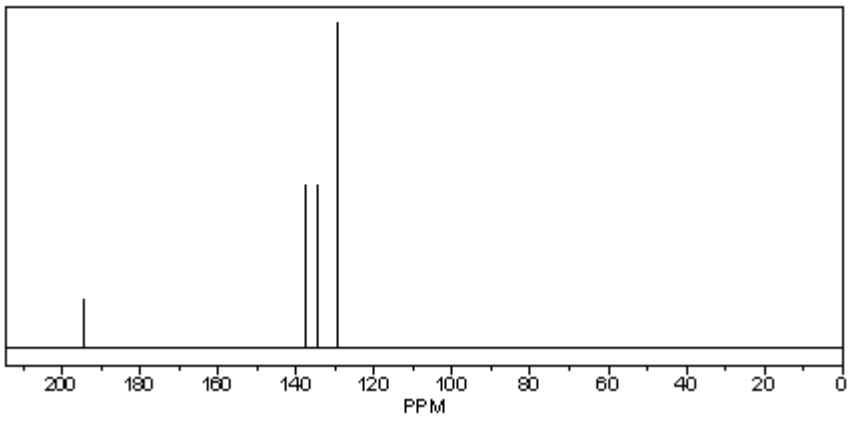
ANNEX

BENZIL









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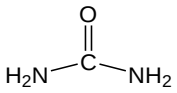
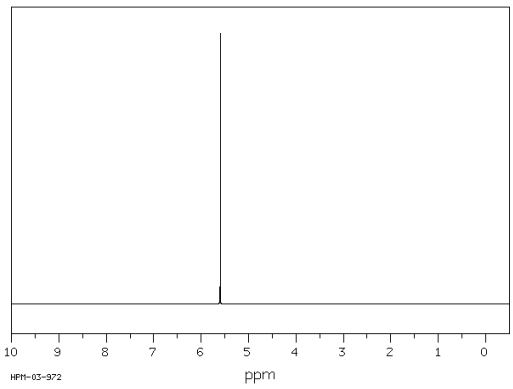
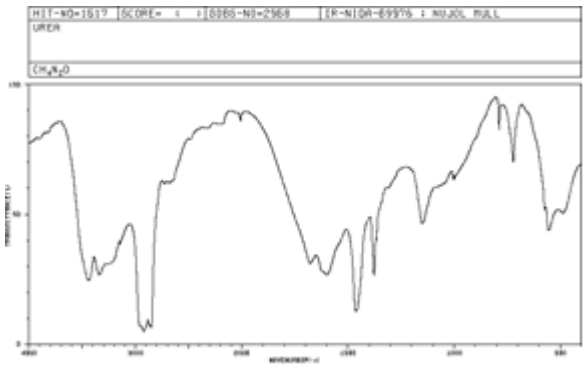
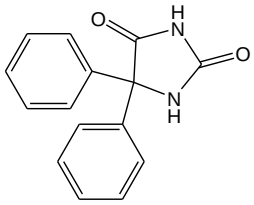


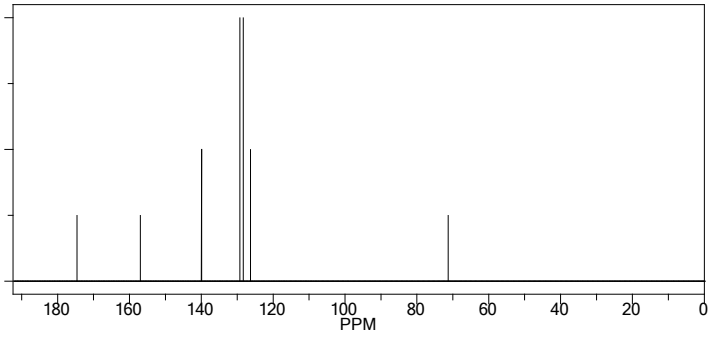


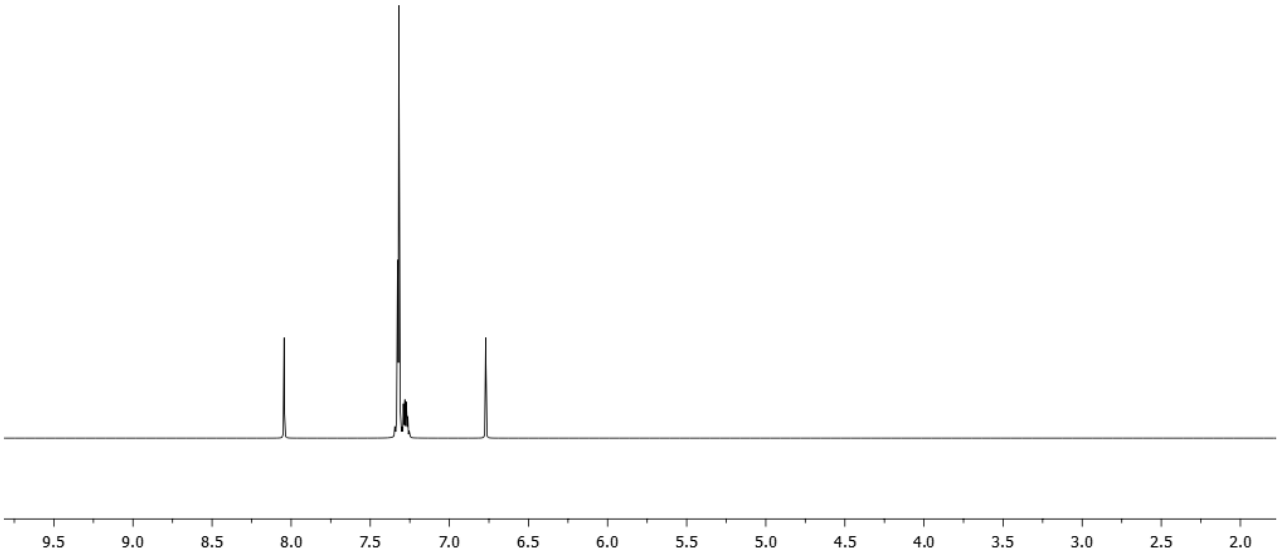


DIPHENYLHIDANTOIN

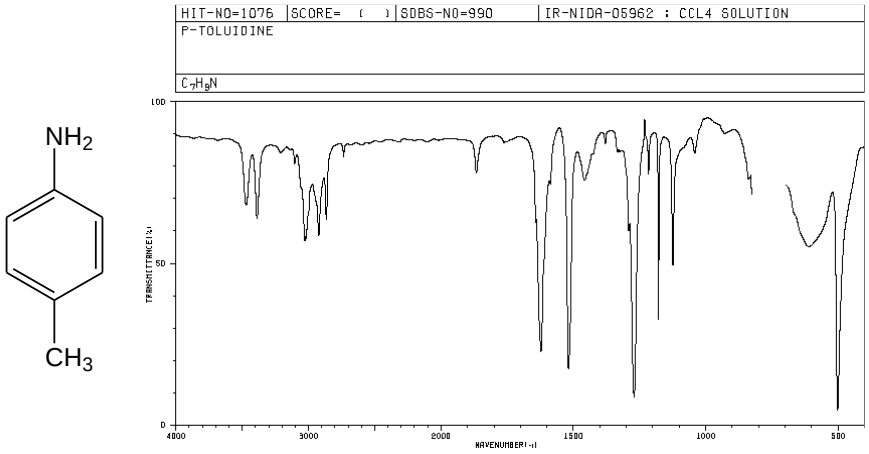


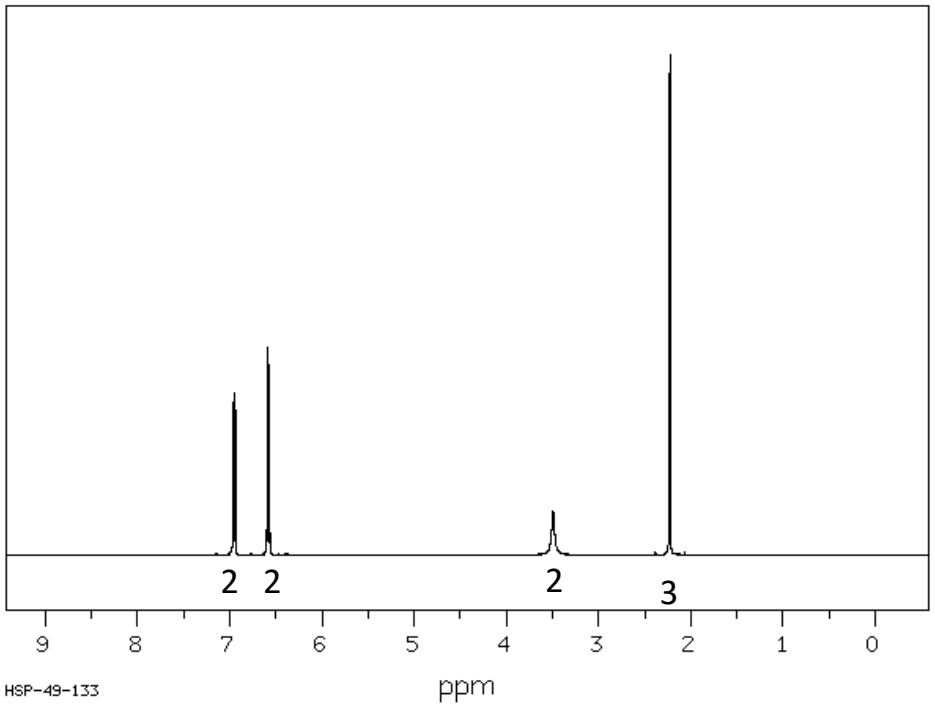
IR spectrum (KBr), ν, cm^{-1}: 3200–3280 s (NH); 1720 s, 1780 s (C=O); 1400 m, 1500 m (C–C_{arom}); 747 m (δ =C–H).

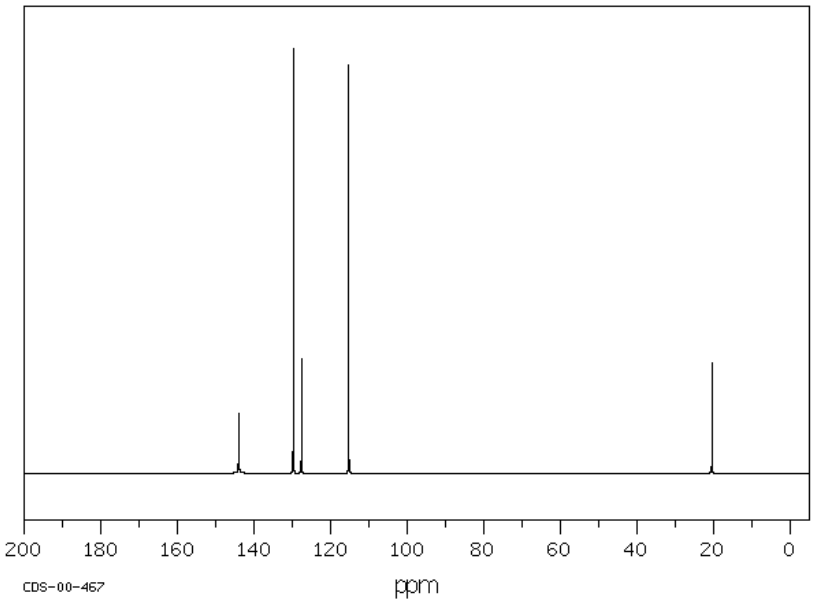




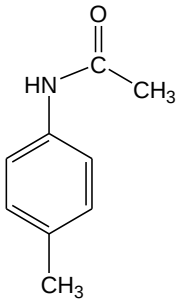
***p*-TOLUIDINE**

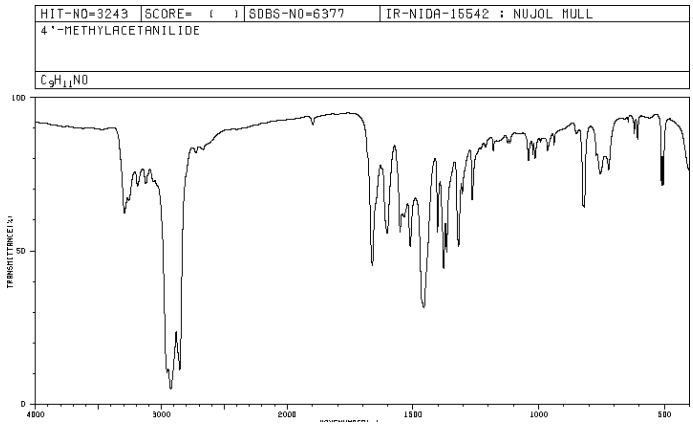


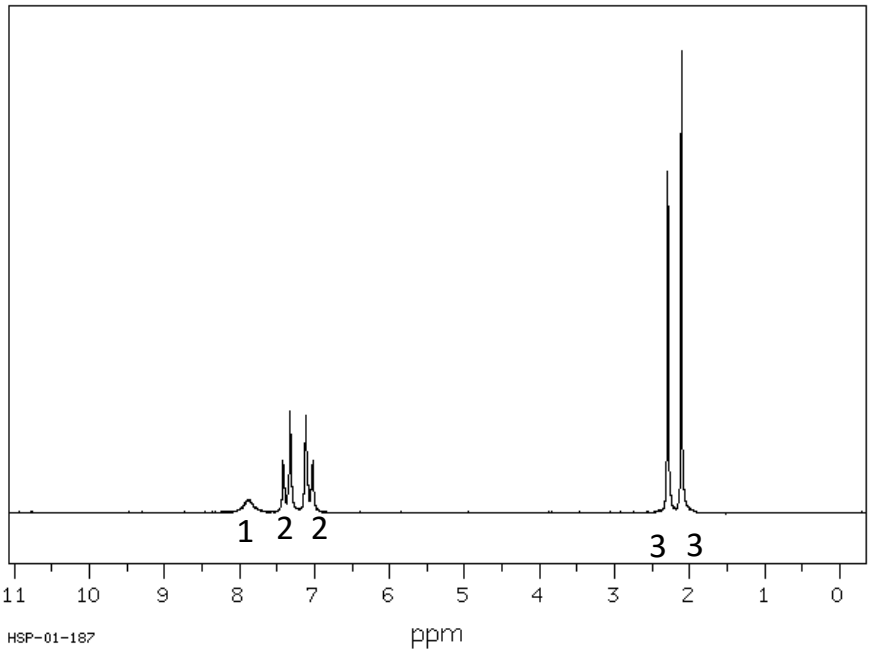


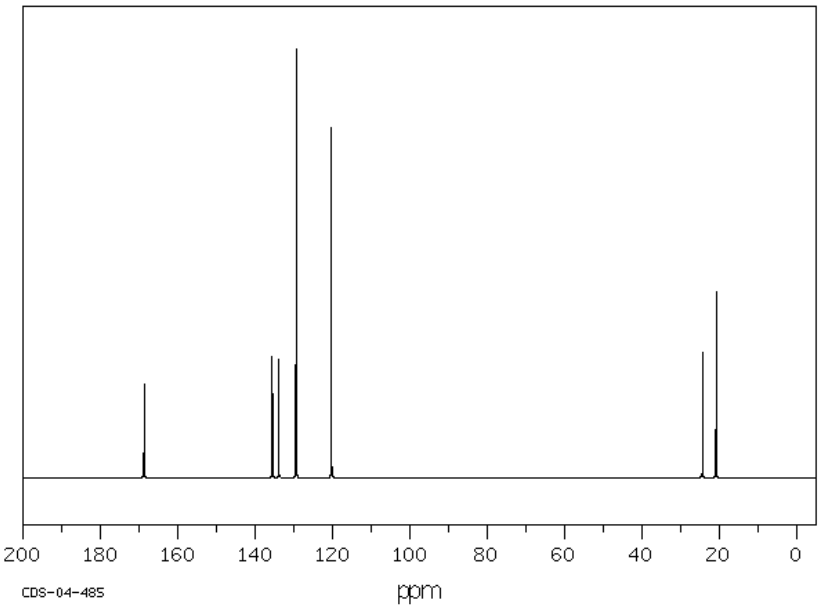


N-ACETYL-*PARA*-TOLUIDINE

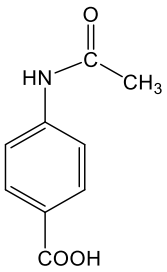








***PARA*-ACETAMIDOBENZOIC ACID**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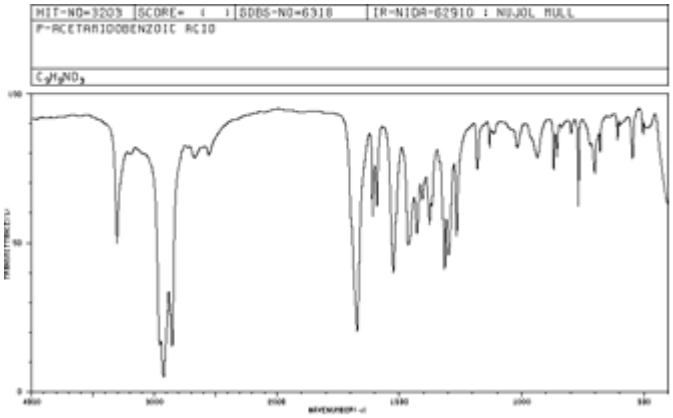
C
CH3
COOH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P-ACETAMIDOBENZOIC ACID
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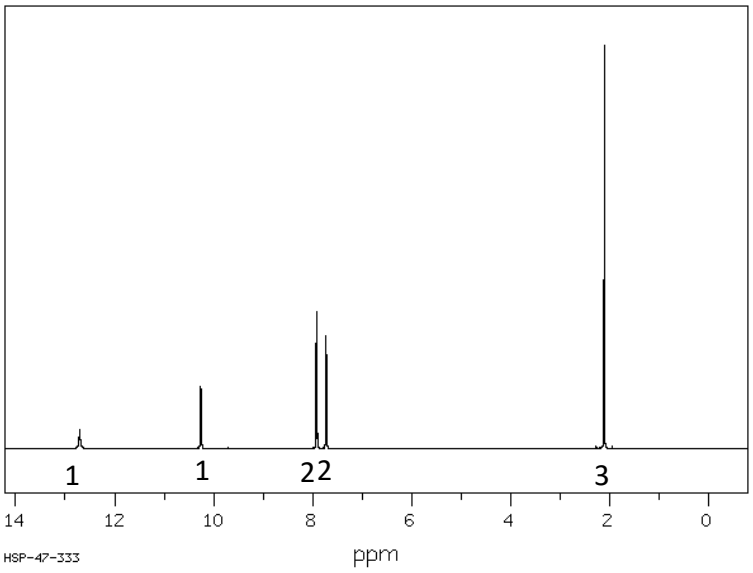
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3
14
12
10
8
6
4
2
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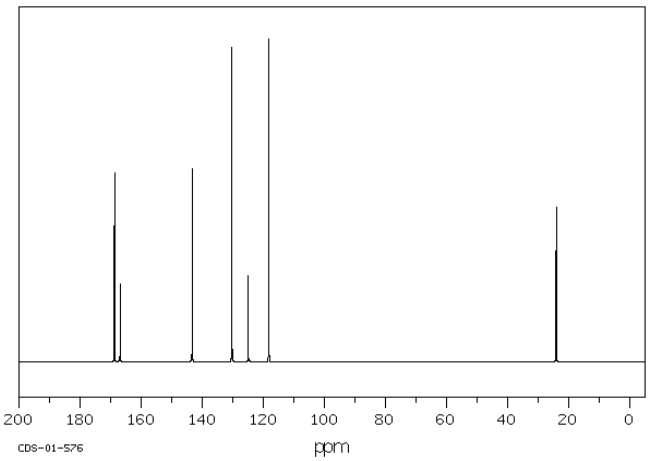
ppm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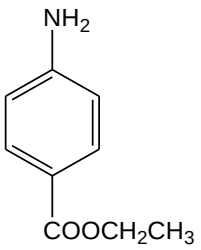

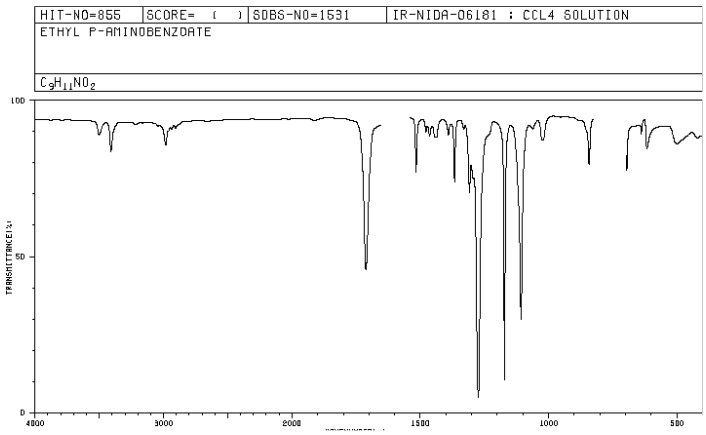

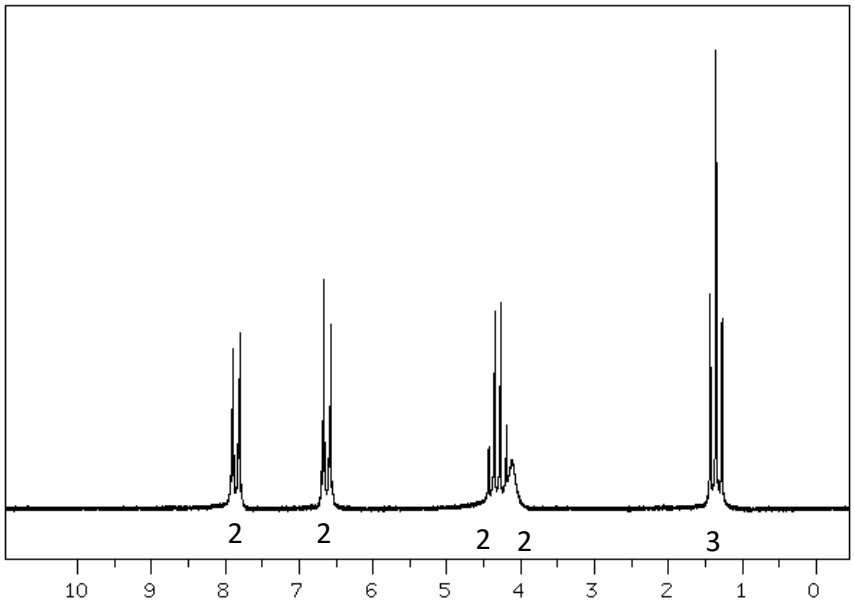

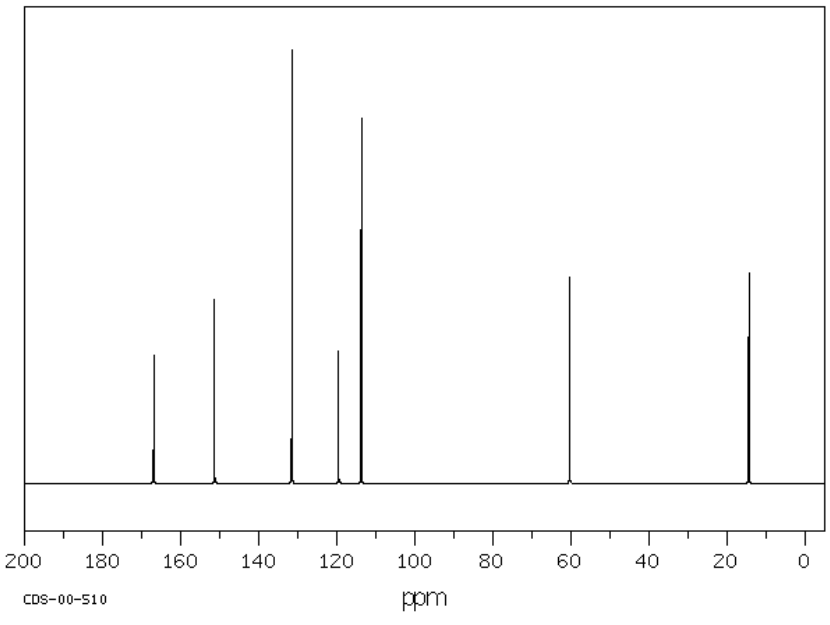

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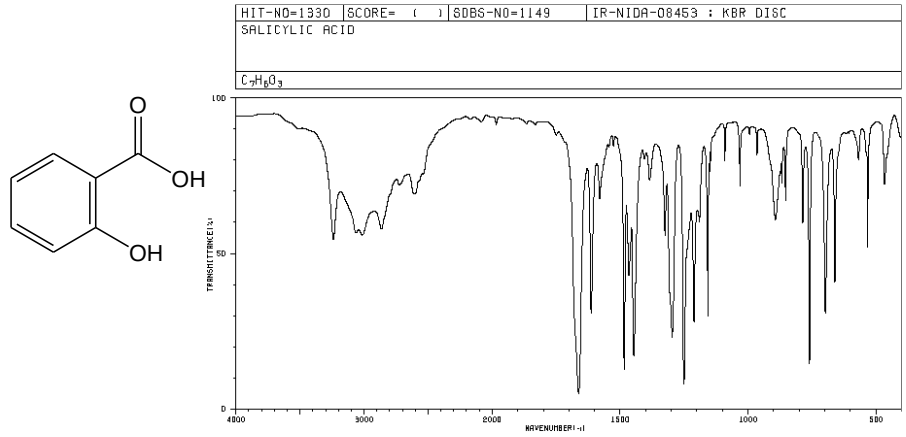
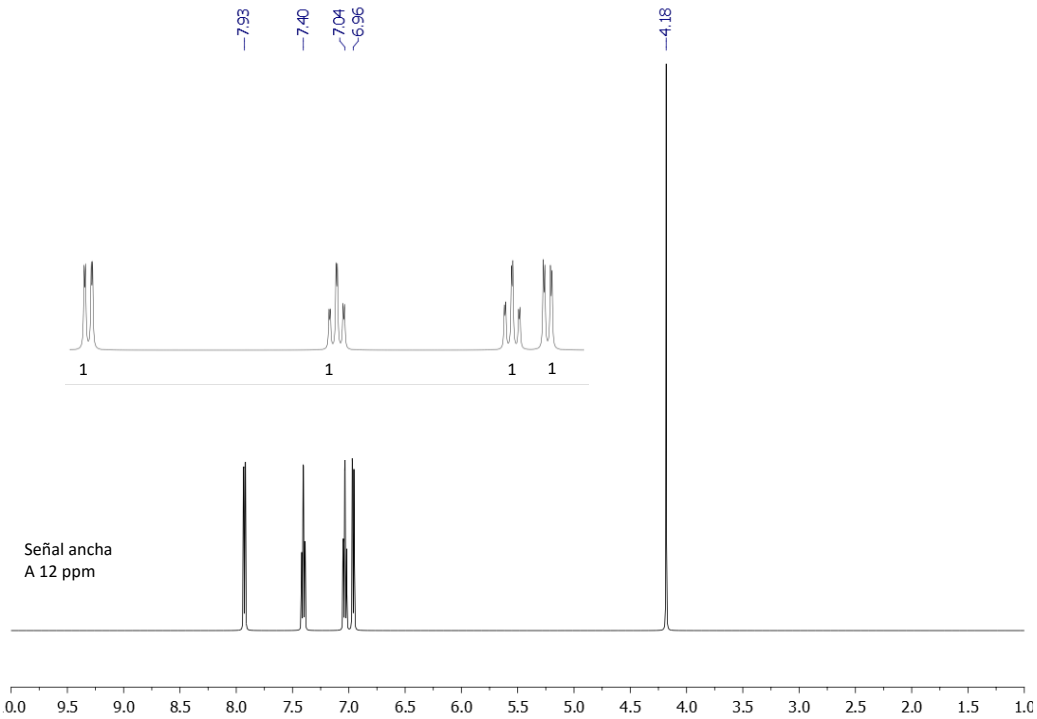
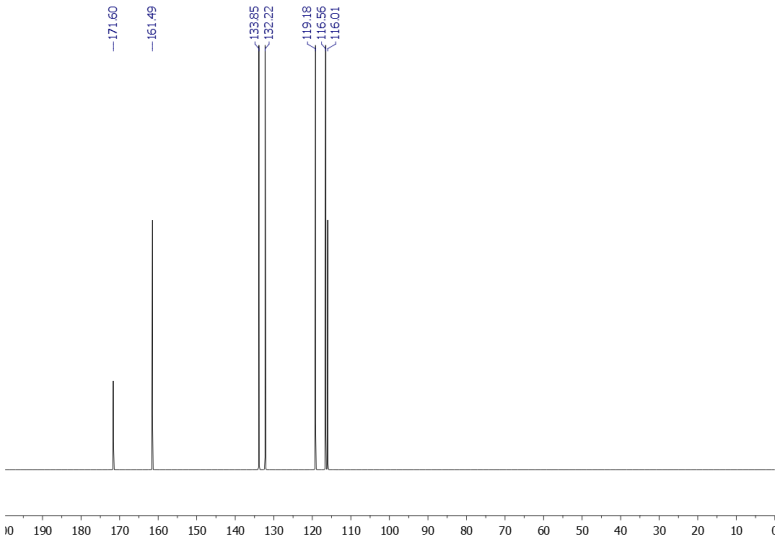
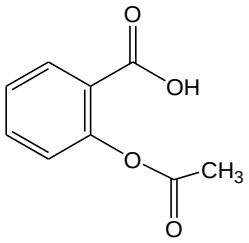






ACETYLSALICYLIC ACID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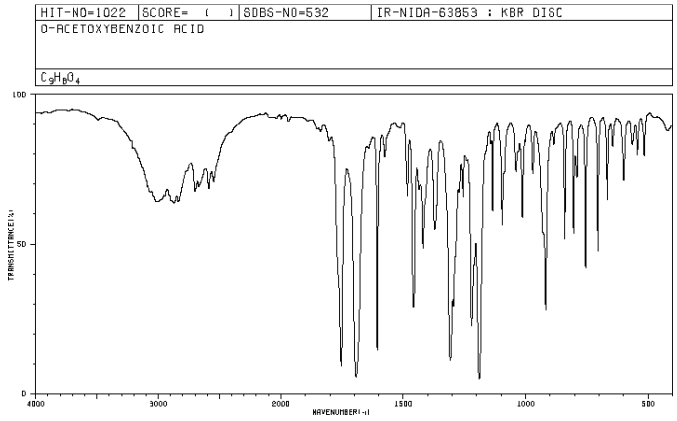
O
CH3
O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SCORE=
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O-ACETOXYBENZOIC ACID
C9H8O4
TRANSMITTANCE[%]
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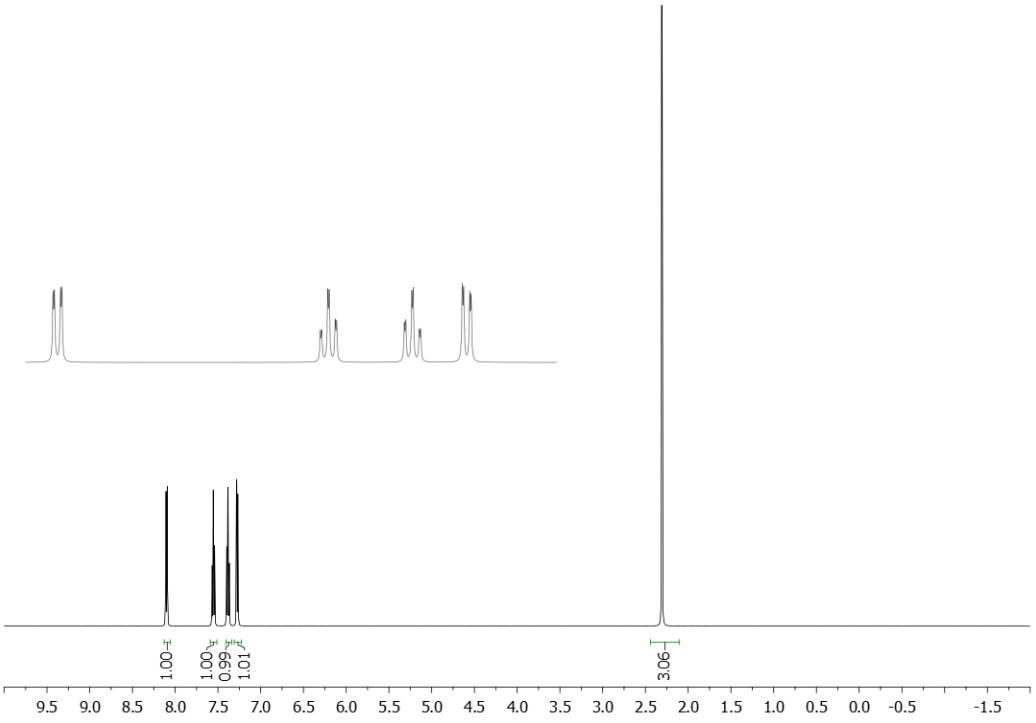
50
0
4000
3000
2000
1500
1000
500
WAVENUMBER[cm-1]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1.00
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3.06
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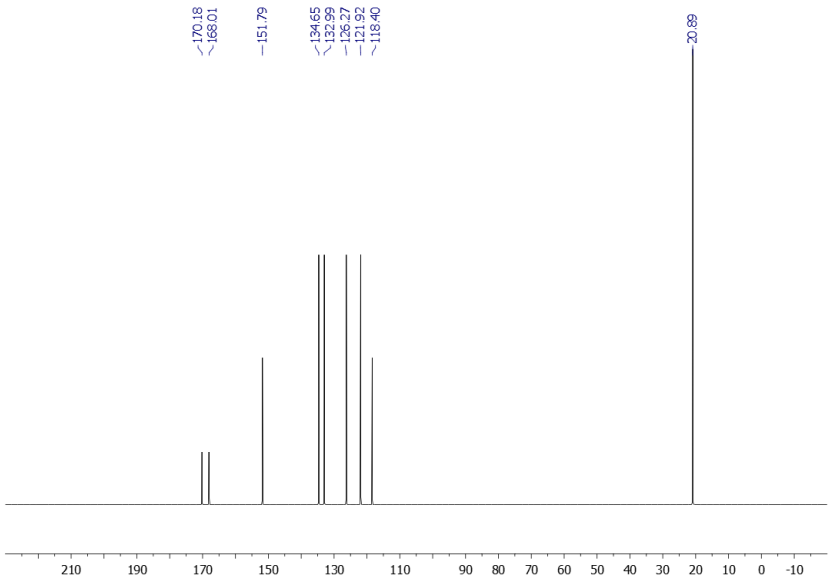
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121.92
118.40
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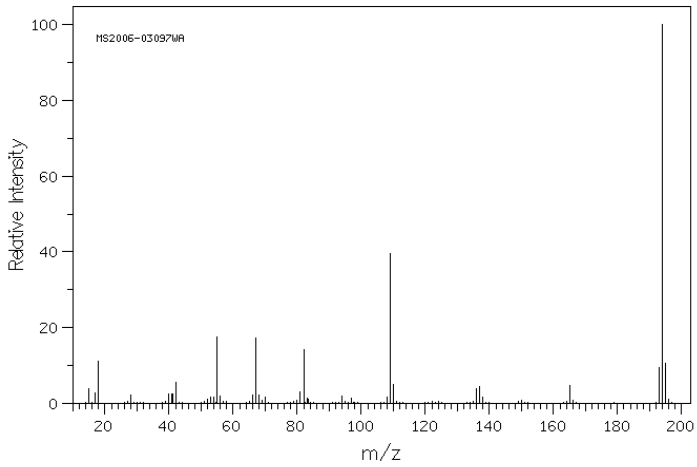
CAFFEINE


O
CH3
H3C
N
N
N
O
N
CH3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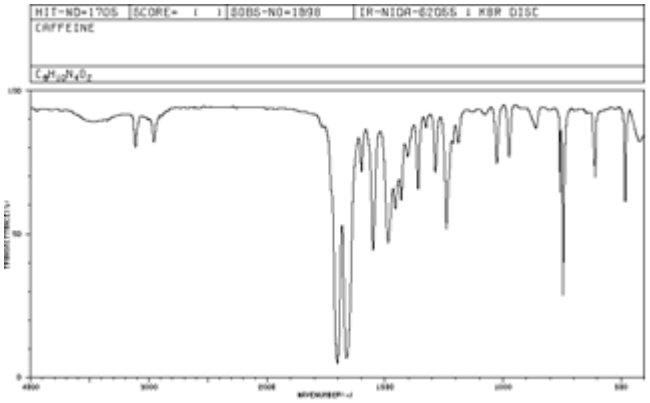
Relative Intensity
m/z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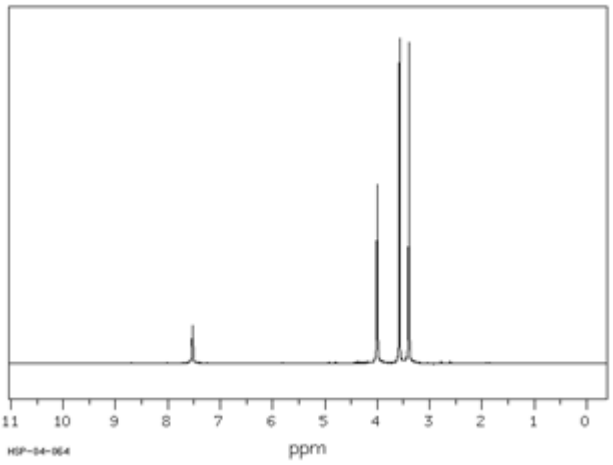
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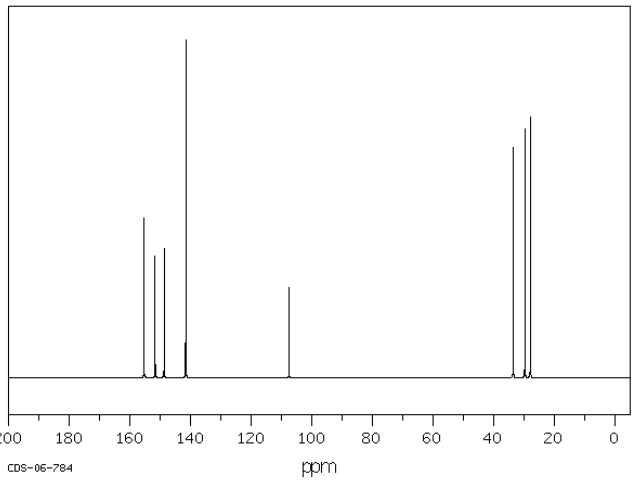
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ppm

Synthesis of the Anticonvulsant Drug 5,5-Diphenylhydantoin

An Undergraduate Organic Chemistry Experiment

Rodney C. Hayward

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The hydantoins are a drug family lying within the broadly related ureide structural frame which encompasses many of the anticonvulsant drugs used in the treatment of the various types of epilepsy. Some examples of this familial relationship are shown in Figure 1.

The hydantoin 5,5-diphenylhydantoin (5,5-diphenyl-2,4-imidazolidinedione; DPH) has diverse effects on the biochemistry of the central nervous system (*1*). However, in the form of its sodium salt (Phenytoin Sodium; e.g., "Dilantin" ®) DPH is of value as an anticonvulsant for the control of grand mal and psychomotor epilepsy.

Commercial access to the drug is direct. It is formed by the treatment of benzophenone with aqueous potassium cyanide and ammonium carbonate (*2*). However, we have used the more pedestrian route to DPA from urea and benzil to enliven the now classic undergraduate synthetic sequence of benzilic acid from benzaldehyde.[1]

The reaction of benzil with urea was studied extensively by Blitz, who recommended this method for the preparation of 5,5-diarylhydantoins (*3*). In a recent study of this reaction (*4*), the pinacolone rearrangement route proposed by Blitz was shown to be untenable for alkaline conditions. It would appear that the adduct of urea anion addition to benzil rearranges in alkaline solution in a matter exactly analogous to the benzil-benzilic acid rearrangement (Fig. 2).

There is a rate-determining attack by the urea anion on one carbonyl group of benzil followed by rapid cyclization and finally, slow rearrangement to the product anion. As in the benzilic acid rearrangement, it is likely that the formation of this latter anion (or the imido-anion) is the driving force behind the rearrangement.

In a typical experiment (see Experimental Section for details) there are potentially two competing reactions of significance:

(1) the formation of benzilic acid from competing hydroxide anion attack on benzil; and
(2) condensation of urea with both carbonyls of benzil in competition with cyclization of the mono-adduct. The product, described by Blitz (*3*) as diphenylacetylene diureide, is formed in variable amounts.

Experimental

Benzil (0.0095 mole)[2] and urea (0.016 mole) are dissolved in 95% ethanol (50 ml). To this solution is then added, all at once, potassium hydroxide (0.047 mole) in water (5 ml). The resulting thick mixture is then warmed gently until a solution is obtained, upon which it is refluxed for 2 hr. At the end of this time the dark-brown solution is cooled and diluted with water (~150 ml). The pale buff colored precipitate (diphenylacetylene diureide)[3] is filtered off and CO_2 is bubbled through the filtrate until precipitation of 5,5-diphenylhydantoin is complete.[4] This is filtered, washed, sucked dry, and recrystallized from the minimum volume of 95% ethanol. A second crop can be obtained from treating the mother liquors with a little charcoal, removal of the ethanol on a rotary evaporator, and recrystallization from a further minimum volume of 95% ethanol. The product is obtained as needles in 50–52% yield, m.p. 297–300° (decomp.); (lit. (*5*) m.p. 295–298°).[5]

Literature Cited

(1) Boykin, M. E., and Doctor, B. P., *J. Pharmacol. Expt. Therap.*, **196**, 469 (1976).
(2) Henze, H. R., U.S. Patent, 2,409,754; *C.A.*, **41**, 1250.
(3) Blitz, H., *Chem. Ber.*, **41**, 1376 (4908); for an extensive review of the early literature see Ware, E., *Chem. Rev.*, **46**, 403 (1950).
(4) Butler, A. R., and Leitch, E., *J. Chem. Soc. Perkin Trans. 2*, 1972 (1977).
(5) "The Merck Index," 9th Ed., Merck & Co. Ltd., Rahway, NJ, 1976, 7130.

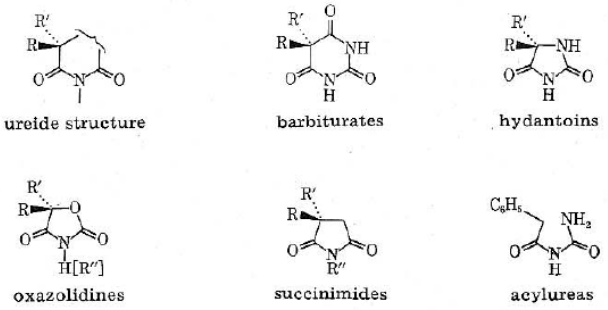

Figure 1. Examples of the hydantoin family of anticonvulsant drugs.

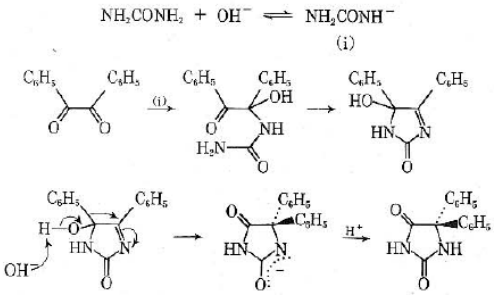

Figure 2. Sequence of reaction of benzil with urea to produce 5,5-diarylhydantoins.

[1] The conversion of benzil into benzilic acid is organic chemistry's most venerable molecular rearrangement being discovered by von Liebig in 1838. von Liebig, J., *Justus Liebigs Ann. Chem.*, **25**, 27 (1838). The benzilic acid rearrangement is a representative of a class of molecular rearrangements of broad scope. For reviews, see: Selman, S., and Eastham, J. F., *Chem. Soc. Quart. Rev.* **14**, 221 (1960); Collins, C. J., and Eastham, J. F. *in "The Chemistry of the Carbonyl Group," Patai, S., (Editor)*, Interscience, London, **1966**.

[2] Prepared from benzaldehyde by any of the standard routes. See Vogel, A. I., "A Textbook of Practical Organic Chemistry," 4th ed., Longman, Inc., New York, **1978**, pp. 806–807.

[3] Formed in small and variable amounts. Recrystallized from dimethylformamide as fine, colorless needles, m.p. 360+°. The exact identity of this compound is unclear at this time.

[4] Due to DPH having a pKa of 8.31 (Agarwal, S. P., and Blake, M. I., *J. Pharm. Sci.*, **57**, 1434 (1968), the addition of CO_2 gas provides a ready method of adjusting the pH to selectively precipitate the product.

[5] Toxicity. The high insolubility and crystallinity of DPH makes it an easily managed product. The estimated fatal dose of DPH in man is 5 g. Dreisbach, R. H., "Handbook of Poisoning," Lange Medical Publishers, Los Altos, California, **1977**.

It is likely that a relationship exists between long-term (2–21 yr) epilepsy management with DPH and increased incidence of lymphoma. It is noteworthy that despite the seriousness of this possible side effect, the conclusion is that the drug should not be withheld if need is indicated, *Lancet*, **ii**, 1071 (1971).