全国高等医药院校药学类实验教材

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药物化学实验

MEDICINAL CHEMISTRY EXPERIMENT

主编 孙铁民

中国医药科技出版社

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Medicinal chemistry Experiment

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内 容 提 要

药物化学实验是药物化学课程的重要组成部分，其目的是通过实验加深对药物化学基本理论和基本知识的理解，掌握当代药物合成的基本方法和对药物进行结构修饰的基本方法，并以创新药物的设计为基本实践。本实验教材以综合实验为主体，突出创新和设计实验的重点。本书的中英文对照内容可以加强学生的专业英语水平。

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编 写 说 明

经教育部和全国高等医学教育学会批准，全国高等医学教育学会药学教育研究会于2004年4月正式成立，全国高等医药院校药学类规划教材编委会归属于药学教育研究会。为适应我国高等医药教育的改革和发展、满足市场竞争和医药管理体制对药学教育的要求，教材编委会组织编写了“全国高等医药院校药学类规划教材”。

本系列教材是在充分向各医药院校调研、总结归纳当前药学教育迫切需要补充一些教学内容的基础上提出编写宗旨的。本系列教材的编写宗旨是：药学特色鲜明、具有前瞻性、能体现现代医药科技水平的高质量的药学教材。也希望通过教材的编写帮助各院校培养和推出一批优秀的中青年业务骨干，促进药学院校之间的校际间的业务交流。

参加本系列教材的编写单位有：中国药科大学、沈阳药科大学、北京大学药学院、广东药学院、四川大学华西药学院、山西医科大学、华中科技大学同济药学院、复旦大学药学院、西安交通大学药学院、山东大学药学院、浙江大学药学院、北京中医药大学等几十所药学院校。

教材的编写尚存在一些不足，请各院校师生提出指正。

全国高等医药院校药学类

规划教材编写办公室

2004年4月16日

前　言

药物化学实验是药物化学课程的重要组成部分，其目的是通过实验加深对药物化学的基本理论和基本知识的理解，掌握当代合成药物的基本方法和对药物进行结构修饰的基本方法，并以创新药物的设计为基本实践。通过本课程的学习可培养学生理论联系实际的作风和创新能力。

为适应21世纪对新一代药物研究人才的要求，本实验教材以综合实验为基础，突出创新和设计实验的重点。同时，本实验教材采用中英文对照编写，可使学生的专业英语水平得以提高。

本实验教材是沈阳药科大学药化教研室长期教学经验的集体总结，是几代药化人集体智慧的结晶，在此对老一代药物化学教师表示崇高的敬意。赵冬梅副教授和蔡志强等多名研究生参与本实验教材部分工作，沈阳药科大学教务处的各位领导给予了大力支持，在此表示感谢。由于作者水平有限，难免有误，欢迎使用本教材的各兄弟院校提出宝贵意见。

编　者

2007年8月

目　录

实验一　阿司匹林的合成

【实验目的】

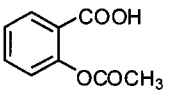
1. 掌握酯化反应和重结晶的原理及基本操作。
2. 熟悉搅拌机的安装及使用方法。

【实验原理】

阿司匹林为解热镇痛药，用于治疗伤风、感冒、头痛、发烧、神经痛、关节痛及风湿病等。近年来，又证明它具有抑制血小板凝聚的作用，其治疗范围进一步扩大到预防血栓形成和治疗心血管疾病。

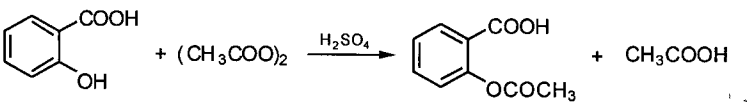
化学名：2－乙酰氧基苯甲酸

化学结构式：



阿司匹林为白色针状或板状结晶，mp.135～140℃，易溶于乙醇，可溶于三氯甲烷、乙醚，微溶于水。

合成路线如下：



【实验步骤】

1. 酯化

在装有搅拌棒及球形冷凝器的100ml三颈瓶中，依次加入水杨酸10g，醋酐14ml，浓硫酸5滴。开动搅拌机，置油浴加热，待浴温升至70℃时，维持在此温度反应30min。停止搅拌，稍冷，将反应液倾入150ml冷水中，继续搅拌，至阿司匹林全部析出。抽滤，用少量稀乙醇洗涤，压干，得粗品。

2. 精制

将所得粗品置于附有球形冷凝器的100ml圆底烧瓶中，加入30ml乙醇，于水浴上加热至阿司匹林全部溶解，稍冷，加入活性炭回流脱色10min，趁热抽滤。将滤液慢慢倾入

75ml热水中，自然冷却至室温，析出白色结晶。待结晶析出完全后，抽滤，用少量稀乙醇洗涤，压干，置红外灯下干燥（干燥时温度不超过60℃为宜），测熔点，计算收率。

3．水杨酸限量检查

取阿司匹林0.1g，加1ml乙醇溶解后，加冷水适量，制成50ml溶液。立即加入1ml新配制的稀硫酸铁铵溶液，摇匀；30s内显色，与对照液比较，不得更深（0.1%）。

对照液的制备：精密称取水杨酸0.1g，加少量水溶解后，加入1ml冰醋酸，摇匀；加冷水适量，制成1000ml溶液，摇匀。精密吸取1ml，加入1ml乙醇，48ml水，及1ml新配制的稀硫酸铁铵溶液，摇匀。

稀硫酸铁铵溶液的制备：取盐酸（1mol/L）1ml，硫酸铁铵指示液2ml，加冷水适量，制成1000ml溶液，摇匀。

4．结构确证

（1）红外吸收光谱法、标准物TLC对照法。

（2）核磁共振光谱法。

【思考题】

1．向反应液中加入少量浓硫酸的目的是什么？是否可以不加？为什么？

2．本反应可能发生哪些副反应？产生哪些副产物？

3．阿司匹林精制选择溶媒依据什么原理？为何滤液要自然冷却？

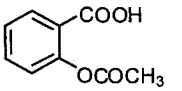
Experiment Ⅰ Synthesis of Aspirin

【Purpose】

1. To master the principle and the basic operation of esterification and recrystallization.
2. To master the use and equipment of the stirrer.

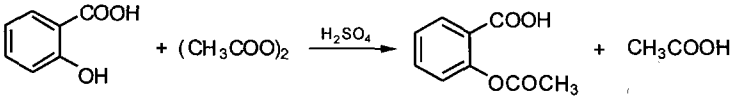
【Principle】

Aspirin is an antipyretic analgesic, which is used in the treatment of cold, headache, fever, neuralgia, arthralgia and rheumatic. Recently, it has been proved that it can restrain the agglomeration of blood platelet, and the scope of its treatment is enlarged to prevent the form of thrombus and cardiovascular disease. The chemical name of Aspirin is 2 – acetoxybenzoic acid, and chemical structure is as follow:



Aspirin is the needle – like or plate crystal, mp.135 ~ 140℃, easily soluble in ethanol, soluble in chloroform and ether, and slightly soluble in water.

The synthetic route is as follow:



【Procedure】

1. The esterification of salicylic acid

In a 100ml three necked flask equipped with a reflux condenser and a stirrer bar, 10g of salicylic acid, 14ml of acetic anhydride and 5 drops of concentrated sulfuric acid were added and was heated to 70℃ with stirring for 30minutes. Then the stirrer was stopped, and the reaction mixture was cooled for a while and was poured into 150ml of cold water. It was con-

tinued to stir until the crystal appeared. Then it was filtered, washed with a little dilute alcohol, and was pressed until it was dry. The crude product was obtained.

2. The refinement of Aspirin

In a 100ml round bottom flask equipped with a spherical condenser, the crude product and 30ml of ethanol were added. It was heated in the water bath until Aspirin was completely dissolved. After cooled for a moment, the active carbon was added and the mixture was discolored with reflux for 30minutes. It was filtrated, poured into 75ml of hot water and was cooled to room temperature naturally. Then all the crystal was precipitated. It was filtrated, washed with a little dilute ethanol, pressed until it was dry. The product was dried under the infrared lamp (the temperature should not exceeded 60℃), and the melting point was measured and the yield was calculated.

3. The limit examination of salicylic acid

0.1g of Aspirin was weighed and dissolved in 1ml of ethanol, sufficient water was added to make the 50ml solution. 1ml of freshly prepared dilute ferric ammonium sulfate solution was added immediately and shook homogeneously. Within 30 seconds, the color of the solution was lighter than that of the contrast solution (0.1%).

The preparation of the contrast solution: 0.1g of salicylic acid was accurately weighed and dissolved in a little water. 1ml of glacial acetic acid was placed and shook. Then some cold water was added to make 1000ml and shook. Sucked 1ml of the solution accurately, added 1ml of ethanol, 48ml of water and 1ml of freshly prepared dilute ferric ammonium sulfate solution and shook it homogeneously.

The preparation of dilute ferric ammonium sulfate solution: add 1ml of hydrochloride acid (1mol/L), 2ml of ferric ammonium sulfate indictor solution and sufficient cold water to make 1000ml and then shook it homogeneously.

4. Identification

(1) Infrared absorption spectrometry, TLC confrontation experiment with standard substance.

(2) Nuclear magnetic resonance spectroscopy.

【Questions】

1. What is the purpose of the addition of a little concentrated sulfuric acid into the reaction mixture?

2. What side reactions will occur? What are the by – products?

3. What is the principle of solvent chosen in the refinement of Aspirin? Why should the filtrate be cooled naturally?

实验二　扑炎痛的合成

【实验目的】

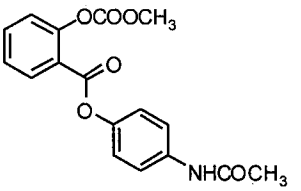
1. 通过乙酰水杨酰氯的制备，了解氯化试剂的选择及操作中的注意事项。
2. 通过本实验了解拼合原理在化学结构修饰方面的应用。
3. 通过本实验了解 Schotten – Baumann 酯化反应原理。

【实验原理】

扑炎痛为一种新型解热镇痛抗炎药，是由阿司匹林和对乙酰氨基酚（扑热息痛）经拼合原理制成，它既保留了原药的解热镇痛功能，又减小了原药的毒副作用，并有协同作用。适用于急、慢性风湿性关节炎、风湿痛、感冒发烧、头痛及神经痛等。

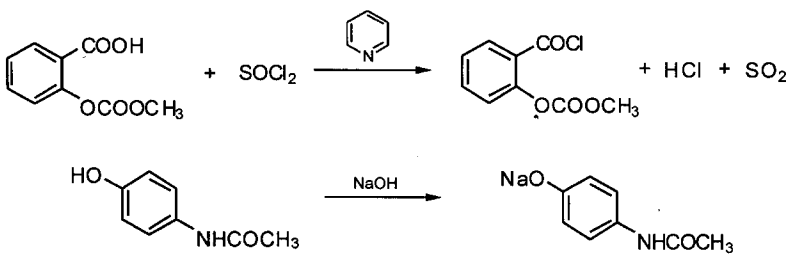
化学名：2 – 乙酰氧基苯甲酸 – 乙酰胺基苯酯

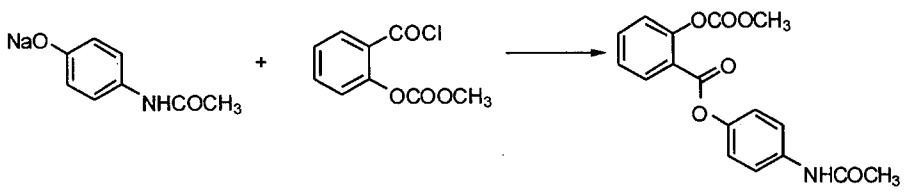
化学结构式：



扑炎痛为白色结晶性粉末，无臭无味。mp.174 ~ 178℃，不溶于水，微溶于乙醇，溶于三氯甲烷、丙酮。

合成路线如下：





【实验步骤】

1．乙酰水杨酰氯的制备

在干燥的 100ml 圆底烧瓶中，依次加入吡啶 2 滴，阿司匹林 10g，氯化亚砜 5.5ml，迅速按上球形冷凝器（顶端附有氯化钙干燥管，干燥管连有导气管，导气管另一端通到水池下水口）。置油浴上慢慢加热至 70℃（约 10～15min），维持油浴温度在 70±2℃反应 70min，冷却，加入无水丙酮 10ml，将反应液倾入干燥的 100ml 滴液漏斗中，混匀，密闭备用。

2．扑炎痛的制备

在装有搅拌棒及温度计的 250ml 三颈瓶中，加入对乙酰氨基酚 10g，水 50ml。冰水浴冷至 10℃左右，在搅拌下滴加氢氧化钠溶液（氢氧化钠 3.6g 加 20ml 水配成，用滴管滴加）。滴加完毕后，在 8～12℃之间，在强烈搅拌下，慢慢滴加上次实验制得的乙酰水杨酰氯丙酮溶液（在 20min 左右滴完）。滴加完毕，调至 pH≥10，控制温度在 8～12℃之间继续搅拌反应 60min，抽滤，水洗至中性，得粗品，计算收率。

3．精制

取粗品 5g 置于装有球形冷凝器的 100ml 圆底瓶中，加入 10 倍量（*W*/*V*）95% 乙醇，在水浴上加热溶解。稍冷，加活性炭脱色（活性炭用量视粗品颜色而定），加热回流 30min，趁热抽滤（布氏漏斗、抽滤瓶应预热）。将滤液趁热转移至烧杯中，自然冷却，待结晶完全析出后，抽滤，压干；用少量乙醇洗涤两次（母液回收），压干，干燥，测熔点，计算收率。

4．结构确证

（1）红外吸收光谱法、标准物 TLC 对照法。

（2）核磁共振光谱法。

【注释】

1．二氯亚砜是由羧酸制备乙酰水杨酰氯最常用的氯化试剂，不仅价格便宜而且沸点低，生成的副产物均为挥发性气体，故所得酰氯产品易于纯化。二氯亚砜遇水可分解为二氧化硫和氯化氢，因此所用仪器均需干燥；加热时不能用水浴。反应用阿司匹林需在 60℃干燥 4h。吡啶作为催化剂，用量不宜过多，否则影响产品的质量。制得的乙酰水杨酰氯不应久置。

2．扑炎痛制备采用 Schotten－Baumann 方法酯化，即乙酰水杨酰氯与对乙酰氨基酚钠

缩合酯化。由于对乙酰氨基酚的羟基与苯环共轭，加之苯环上又有吸电子的乙酰胺基，因此酚羟基上电子云密度较低，亲核反应性较弱；成盐后酚羟基氧原子电子云密度增高，有利于亲核反应；此外，酚钠成酯，还可避免生成氯化氢，使生成的酯键水解。

【思考题】

1. 乙酰水杨酰氯的制备，操作上应注意哪些事项？

2. 扑炎痛的制备，为什么采用先制备对乙酰胺基酚钠，再与乙酰水杨酰氯进行酯化，而不直接酯化？

3. 通过本实验说明酯化反应在结构修饰上的意义。

Experiment Ⅱ Synthesis of Benorylate

【Purpose】

1. Through the preparation of salicylaldehyde chloride to comprehend the choice of chlorination reagent and the notes in the operation.

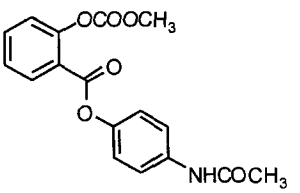
2. Through the experiment to comprehend the application of piecing together principle in chemical structure modification.

3. Through the experiment to master the mechanism of Schotten – Baumann esterification reaction.

【Principle】

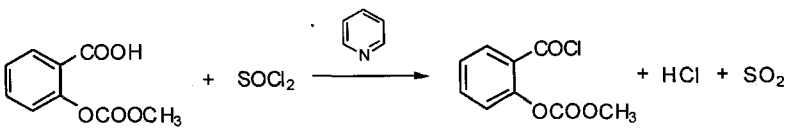
Benorylate is a new antipretic, analgesics, counterplea medicine, and is synthesized by piecing together principle of Aspirin and paracetamol. It retains the original antipyretic analgesic drug function, reduces the original drug toxicities, and synergies. Applicable to the acute and chronic rheumatic arthritis, rheumatism and cold fever, headache and neuralgia, and so on.

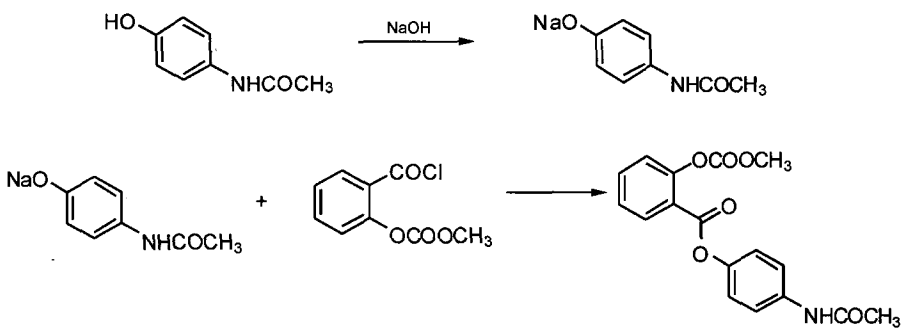
The chemical name of Benovylate is 2 – acetyl – p – phenyl ester Acetamide, and chemical structure is as follow:



Benorylate is a white and crystal powder, odorless and tasteless. mp. 174 ~ 178℃, it is insoluble in water, slightly soluble in ethanol and dissolve in chloroform, acetone.

The synthetic route is as follow:





【Procedure】

1. Synthesis of salicylaldehyde chloride

In a dried 100ml conical flask, followed by adding two drops of pyridine, 10g of aspirin, 5.5ml of thionyl chloride, quickly place the spherical condenser on it (top equipped with calcium chloride drying tube which is connected to airways, whose other end links to pool sewer). It was heated to 70℃ in the oil bath, (about 10 ~ 15min), and the temperature was kept at 70 ± 2℃ for 70min, cooled, and 10ml of anhydrous acetone was added the reaction solution, then poured a dried 100ml dropping funnel, standby.

2. The preparation of Benorylate

In a 250ml three necked flask equipped with stirrer and thermometer, 10g of paracetamol and 50ml of water were added. It was cooled to 10℃ in ice water bath, and sodium hydroxide solution was added under stirring (3.6g of sodium hydroxide was added to 20ml of water using dropping funnel). After that, the solution of acetyl salicylic chloride and acetone solution prepared above was added dropwise under vigrous stirring at 8 ~ 12℃ (about 20min). After that, the pH of the solution was adjusted to ≥10, the temperature was controlled at 8 ~ 12℃ for 60 minutes, filtrated, washed with water, the yield was calculated.

3. Refinement

5g of crude product was added into a 100ml conical flask equipped with spherical condenser, and 10 volume folds (w/v) 95% ethanol was added to it, heated to dissolve in water bath. Cooled the reaction mixture, and active carbon was added to bleach (depending on crude color to determine the amount of activated carbon), refluxed for 30min and filtrated (Brinell funnel and bottles should be preheated). The filtration was transferred to a beaker, cooled. After crystallization precipitated completely, filtrated, pressure dried; washed twice with a small amount of ethanol (from waste liquid), dried, the melting point was measured and the yield was calculated.