全国高等教育药学类规划教材

QUANGUO GAODENG JIAOYU YAOXUELEI GUIHUA JIAOCAI

药物化学实验双语教程

Experiments of Medicinal Chemistry

李　雯　刘宏民　主编

尤启冬　主审

化学工业出版社

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·北京·

《药物化学实验双语教程（Experiments of Medicinal Chemistry）》按照从基础操作到综合实验的顺序安排了10个经典化学药物合成实验，强调了药物化学理论教学与实验的关联，关注学生实验能力和科研素质的培养。附录包含实验报告模板、常规仪器和思考题参考答案三部分内容。

《药物化学实验双语教程（Experiments of Medicinal Chemistry）》可作为高等医药院校药学类专业学生（包括留学生）的实验教材，也可供其他药学相关专业从业人员参考使用。

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序

随着我国教育国际化进程的发展，高等教育的国际化已由原有的单纯“走出去”，逐渐转变为“走出去”和“招进来”相结合的模式。越来越多的外国留学生，特别是“一带一路”沿线国家和亚非等国的外国留学生到中国来学习。但我国双语教材的建设速度与日益增多的留学生发展趋势不能同步，因此，进行双语教材的编写和推广使用工作有着非常重要的价值和意义。

郑州大学药学院根据药学专业中国学生双语教学的需求和留学生教学的需求，开展实验教学研究，编写和出版了《药物化学实验双语教程（Experiments of Medicinal Chemistry）》。

该教材重视加强学生科研能力的培养，是作者针对国内学生和留学生的实际情况，分析现行各版本教材的内容和特点，博采众家所长而编写的教材，具有以下特色：

（1）在实验原理部分，增加主要原料和产物的物性常数，包括分子量、熔点、沸点和溶解度等参数，以培养学生通过思考和实验操作，触类旁通，提高解决问题的能力，且配以图表便于理解。

（2）增加安全提醒内容，以预防部分学生对危险化学品的错误使用而造成严重后果。

（3）在实验操作方面，增加实验装置图示，以方便学生以直观的方式尽快理解实验操作过程。

（4）增加药物受体和配体相互作用的计算机模拟图示，体现了实验课程对理论课程知识的综合应用和拓展。

（5）为培养学生对实验现象规范记录和结果分析能力，本教材提供了实例并提出了具体的要求，使学生进一步联系理论，做出分析比较。

（6）增加思考题的参考答案，给学生一些提示，方便更好地理解实验相关问题，有助于培养学生的学习兴趣。

相信本教材的出版能够促进我国药物化学实验双语教学的发展。

尤启冬

（国家实验教学示范中心联席会药学学科组组长、国家教学名师）

2019 年 3 月

前　言

为适应我国本科教学国际化的发展趋势，根据药物化学实验课程的基本要求，结合我们多年的教学经验和科研工作，编写了这本《药物化学实验双语教程（Experiments of Medicinal Chemistry）》。

本书包括10个化学药物合成实验，实验一至实验八为我们多年药物化学实验教学实践的总结，实验九和实验十为编者科研工作的结果。在化学药物合成实验的安排上，本书按照从基础操作到综合实验的顺序进行编写；在内容上，本书不仅给出了实验原理、操作过程、注意事项和思考题，而且给出了药物分子和靶标的作用机制图示、主要原料和中间体的物理常数、实验装置、安全提示和思考题参考答案。旨在强调药物化学理论教学与实验的关联，关注学生实验能力和科研素质培养。10个化学药物合成实验的难易程度和实验学时有明显的区分度，可满足不同专业和不同层次学生的教学需求。

本教材的实验一、实验二、实验七、实验九由李雯、刘宏民编写，实验三、实验四由陈亚静编写，实验五由丁丽娜编写，实验六由张恩编写，实验八由郑一超编写，实验十由张秋荣编写，全书由尤启冬教授审订。书中药物分子和靶标的作用机制部分由丁丽娜及其研究生阎影、马超亚、王志正、高琦冰、孙旭东和杨晶等借助MOE软件进行模拟研究编写而成。留学中国的博士研究生Moges Dessale Asmamaw、研究生常英杰、李瑞鹏及本科生朱林元参与了本书的语言润色工作。药物化学实验双语教材的建设，任重而道远。

《药物化学实验双语教程（Experiments of Medicinal Chemistry）》采用中英双语体系编写，可作为普通高等医药院校药学类各专业学生（包括留学生）的实验教材，也可供其他药学相关专业师生参考使用。

编者

2019年3月

Preface

In order to adapt to the development trend of internationalization of undergraduate teaching in our country, according to the basic requirements of pharmaceutical chemistry experiment course combined with our years of teaching experience and scientific research work, this "bilingual course of pharmaceutical chemistry experiment" has been compiled.

In this textbook, 10 synthetic experiments of chemical drugs are included. Experiments 1 through 8 are the summaries of many years teaching practices, Experiments 9 and 10 are the results of the editors' scientific research work. They are arranged by the order from basic to comprehensive gradually. In each experiment, more than the experiment principle, operation process, notes and discussion questions are given, the action mechanism diagrams of drug molecule and target, physical constants of key raw materials and intermediates, experimental equipments, safety tips and reference answers of discussion questions are described. This textbook emphasizes the relationship between theoretical teaching and experiment of pharmaceutical chemistry, and pays attention to the cultivation of students' experimental ability and scientific research quality. There is a clear distinction between the difficulty and time of 10 experiments to meet the teaching needs of students from different majors and levels.

Experiments 1, 2, 7 and 9 of this textbook were written by Wen Li and Hongmin Liu, Experiments 3 and 4 by Yajing Chen, Experiment 5 by Lina Ding, Experiment 6 by En Zhang, Experiment 8 by Yichao Zheng and Experiment 10 by Qiurong Zhang. This textbook was revised by Professor Qidong You. The mechanistic studies between the drug molecule and the corresponding target were investigated and written by Lina Ding and her graduate students Ying Yan, Chaoya Ma, Zhizheng Wang, Qibing Gao, Xudong Sun and Jing Yang with the help of MOE software. We appreciate the foreign PhD student Moges Dessale Asmamaw, graduate students Yingjie Chang, Ruipeng Li and undergraduate student Linyuan Zhu who involved in the language correction of this textbook. The construction of bilingual textbooks is on the developing way.

This textbook is compiled in a Chinese-English bilingual system and can be used in the experimental teaching of pharmaceutical students (including foreign students) in medical colleges and universities.

Editors

March 2019

Contents
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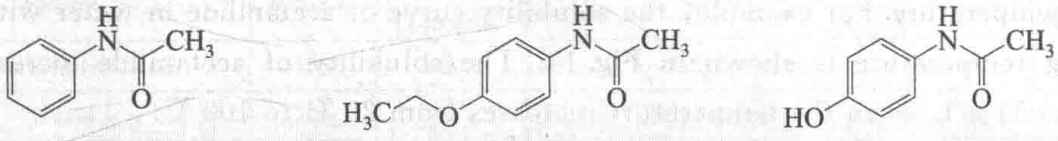
Experiment 1

Recrystallization of Acetanilide

Background

Acetanilide (Fig. 1-1) has an odourless solid chemical of leaf or flake-like appearance. It is also known as *N*-phenylacetamide, acetanil, or acetanilid, and was formerly known as the trade name Antifebrin.

Acetanilide was the first aniline derivative which was found to possess analgesic and antipyretic properties, and was quickly introduced into the medical practice by A. Cahn and P. Hepp in 1886. But due to the unacceptable toxic effects, it has been replaced by a new generation of acetyl drugs such as Phenacetin and Paracetamol (Fig. 1-1).



Acetanilide　　Phenacetin　　Paracetamol

Fig. 1-1　Chemical structures of Acetanilide, Phenacetin and Paracetamol

Now, Acetanilide is mainly used as industrial rubber vulcanization promoters, stabilizers of fiber fat coatings, stabilizers of hydrogen peroxide and for the synthesis of camphor.

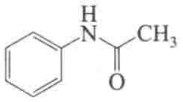
Acetanilide belongs to non-steroidal anti-inflammatory drug (NSAIDs) which general target the cyclooxygenase and lipoxygenase enzymes. The possible binding mode of acetanilide with cyclooxygenase 2 (COX-2) (PDB: 5F1A) is illustrated by **Color Diagram 1**. The acetyl group in the acetanilide forms a hydrogen bond with the oxygen of the hydroxy in the Ser 530 side chain and the benzene ring forms hydrophobic interactions with the surrounding hydrophobic residues.

Ⅰ Purposes and Requirements

1. To master the recrystallization principle.
2. To master the operation of recrystallization.
3. To understand the interaction between acetanilide and target.

Ⅱ Experimental Principle

1. Physical data of the main reactants and product

Name	Structure /CAS No.	Formula /M. Wt	b. p. or m. p. /℃	Solubility/(g/L)
Acetanilide	 103-84-4	C_8H_9NO 135.16	m. p. 113～115	In water: 5.5 (at 100 ℃) and 0.46 (at 20 ℃) In ethanol: 36.9 (at 20 ℃) In methanol: 69.5 (at 20 ℃) In chloroform: 3.6 (at 20 ℃)

2. Recrystallization principle

Compounds obtained from reaction mixtures always contain some impurities. The impurities may include some residues of soluble, insoluble and colored compounds. To obtain a pure product, these impurities must be completely removed.

Recrystallization is the primary method for purifying solid organic compounds. The principle of recrystallization is that the amount of solute that can be dissolved in a solvent increases with temperature. For example, the solubility curve of acetanilide in water with respect to varying temperature is shown in Fig. 1-2. The solubility of acetanilide increases from 4.6 g/L to 55 g/L when the temperature increases from 20 ℃ to 100 ℃.

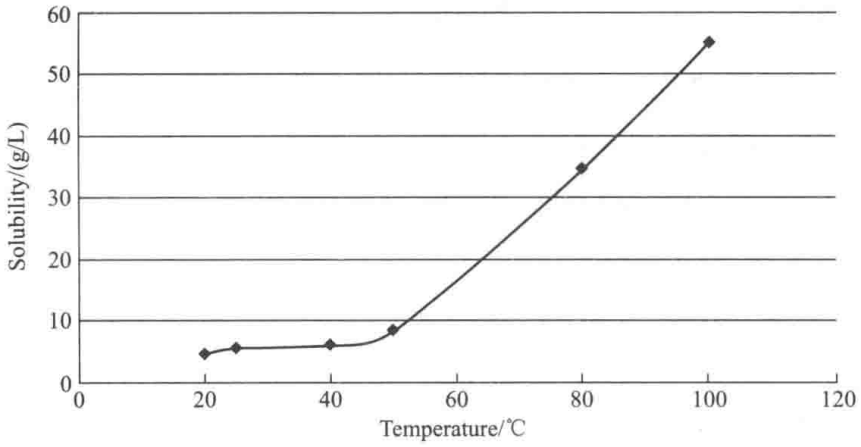


Fig. 1-2 Solubility curve of acetanilide in water

In a recrystallization procedure (Fig. 1-3), selection of an appropriate solvent is the most important factor. When an appropriate solvent is selected, solid compounds which contain some impurities can dissolve in the solvent at or near their boiling points. The insoluble impurities can be removed by hot filtration. This step of recrystallization should be conducted

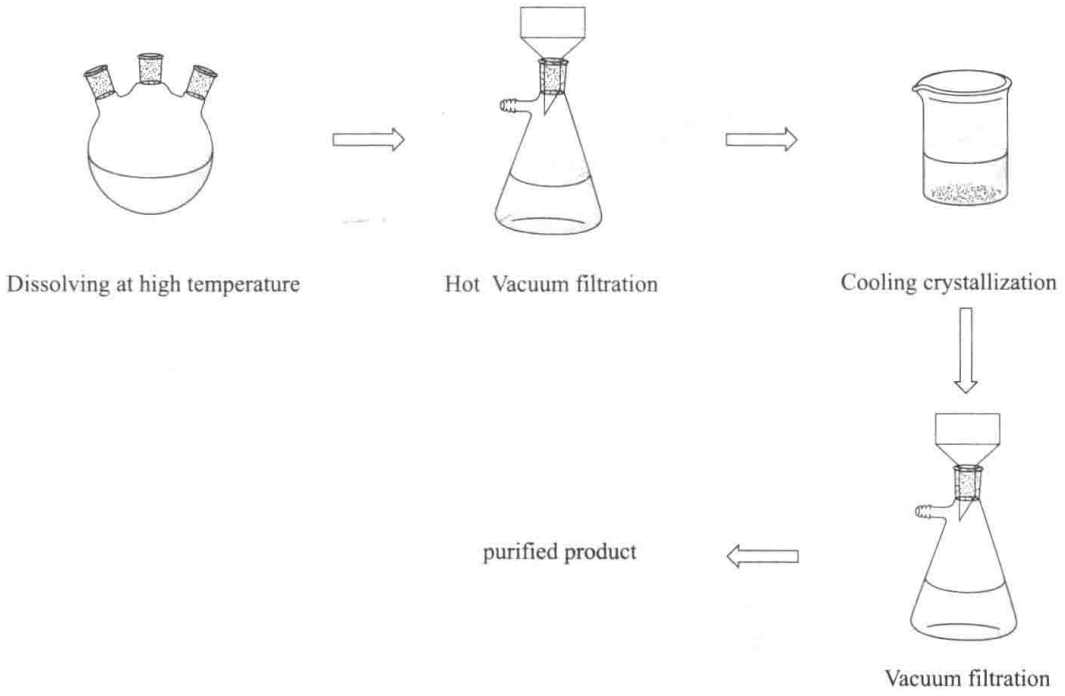


Fig. 1-3 Procedure of recrystallization

while keeping the filtration set-up hot so as to prevent premature crystal formation. Next, allow the hot solution to cool down to the room temperature before collecting the purified crystals by filtration. Note that the soluble impurities will remain in the filtrate.

The boiling points and dielectric constants of the commonly used solvents are summarized in Table 1-1 below.

Table 1-1 The boiling point and dielectric constant of the commonly used solvents

Solvent	b. p. /℃	Dielectric Constant*	Solvent	b. p. /℃	Dielectric Constant*
N-Methylformamide	183	182.4	Tetrahydrofuran	66	7.6
Water	100	78.4	Ethyl acetate	78	6.0
Dimethylsulfoxide	189	46.5	Chloroform	61.2	4.8
N,*N*-Dimethyl-formamide	153	36.7	Diethylether	34.4	4.2
Methanol	64.5	32.7	Toluene	110.6	2.4
Ethanol	78	24.5	Cyclohexane	81	1.9
Acetone	56	20.6	*n*-Heptane	98.4	1.9
2-Methyl-2-propanol, *t*-Butanol	82.3	12.5	*n*-Hexane	68.7	1.9
1,2-Dichloroethane	83.5	10.4	*n*-Pentane	36.1	1.8
Dichloromethane	39.6	8.9			

* The dielectric constant is a measure of the solvent's ability to separate ions. In general, ionic compounds are more soluble in solvents with high dielectric constants.

Ⅲ Experimental Equipments and Raw Materials

1. Experimental equipments

Dissolving set-up is shown in Fig. 1-4. This experimental set-up is composed from three-

neck round-bottom flask, spherical condenser tube, magnetic stirrer and thermometer.

Vacuum filtration set-up is shown in Fig. 1-5. This experimental set-up is composed from filter flask, Buchner funnel, filter paper and vacuum pump.

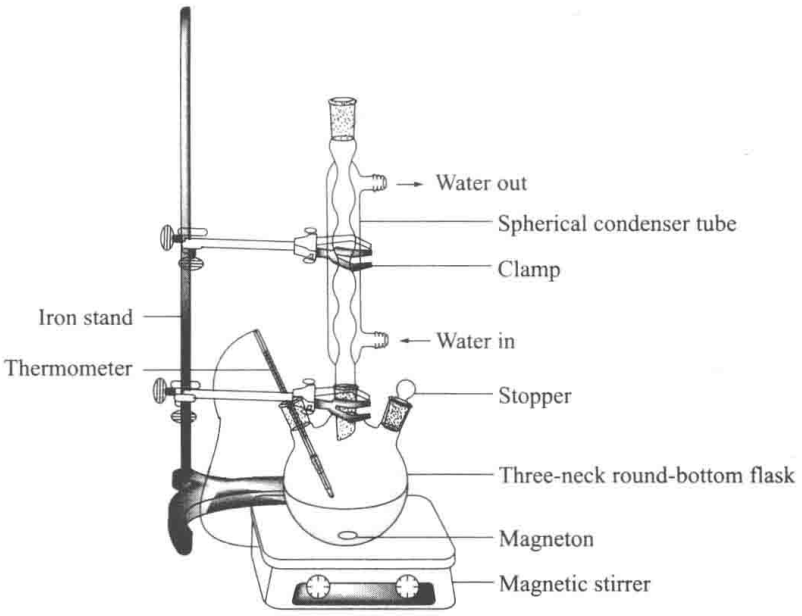


Fig. 1-4 Dissolving set-up

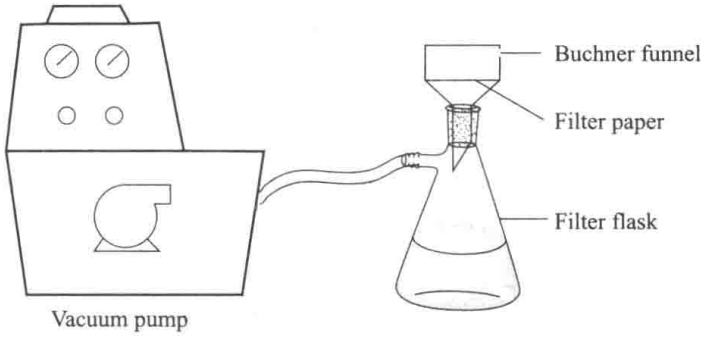


Fig. 1-5 Vacuum filtration set-up

2. Raw materials

Name	Quantity	Quality	Use
Acetanilide	2 g (0.015 mol)	Industrial grade	Raw material
Activated carbon (Charcoal)	0.5 g	—	Decolorizing substance
Distilled water	40 mL	—	Recrystallization solvent

Ⅳ Operations

(1) Equip the dissolving set-up as shown in Fig. 1-4. Add 2 g of the impure acetanilide and 40 mL of distilled water into the 100 mL three-neck round-bottom flask. Dissolve the solute completely by stirring (magnetic stirrer) and heating up the mixture to 100 ℃.

(2) Once acetanilide is dissolved completely, slightly cool down the solution to about 95 ℃ followed by the addition of 0.5 g of activated carbon. Decolorization is achieved by heat-

ing the mixture for about 10 minutes for gentle refluxing.

(3) Equip the vacuum filtration set-up as shown in Fig. 1-5. Filter the hot solution by vacuum filtration. Allow the filtrate to cool down to room temperature in an ice-water bath for about 10 minutes. Caution should be taken not shaking or stirring the filtrate.

(4) The pure product is collected by filtrating again. Attention should be paid to drain the solvent as far as possible.

(5) The product is dried under infrared lamp. Weigh the pure product, calculate the yield and measure the melting point.

(6) Send the final product to the place where the guide teachers designated.

Ⅴ Experimental Results

1. Yield

Calculate the percent yield of acetanilide.

$$\text{Yield}=\frac{\text{Practical production}}{\text{Theoretical production}}\times 100\%=\frac{(\quad)}{2\text{ g}}\times 100\%=(\quad)\%$$

2. Appearance and melting point of the pure product

A. Appearance: _____;

B. m. p. :

Theoretical value: 113～115 ℃;

Practical value: _____.

3. Analysis of experimental results

_____

_____

_____

_____

_____

_____

_____.

Ⅵ Notes

1. In general, the amount of activated carbon is 1%～5% (by weight) of the crude product according to the color depth.

2. Adding activated carbon while the solution is boiling can easily cause serious bumping. Therefore, when the activated carbon is added, the temperature of the solution must be slightly lower.

3. The filtrate of the hot solution should be allowed to cool slowly to room temperature. Gradual cooling is conducive to the formation of large well-defined crystals.

4. When the crystals are collected and washed, allow the water pump to run for several

minutes so that the crystals have an opportunity to dry.

Ⅶ Discussion Questions

1. Why the activated carbon can not be added to the boiling solution when it used as a decolorizing agent?

2. What are the commonly used recrystallization solvents?

(By Wen Li, Hongmin Liu)

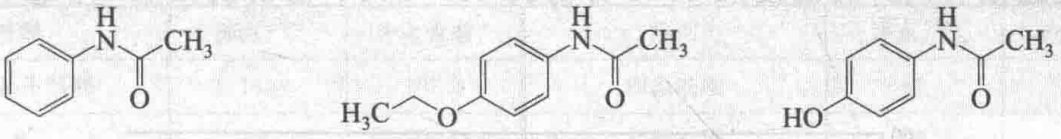
实验一

乙酰苯胺重结晶

背景知识

乙酰苯胺（Acetanilide）为无味，白色叶状或片状结晶（图 1-1）。也称作 *N*-苯基乙酰胺，曾以商品名退热冰应用于临床。

乙酰苯胺是第一个被发现的具有镇痛和解热作用的苯胺类衍生物，1886 年，A. Cahn 和 P. Hepp 将其应用于临床。但是，乙酰苯胺具有严重的副作用从而被新一代的乙酰苯胺类药物取代，比如非那西汀和对乙酰氨基酚。



乙酰苯胺　　非那西汀　　对乙酰氨基酚

图 1-1　乙酰苯胺、非那西汀和对乙酰氨基酚的化学结构式

目前，乙酰苯胺主要用作工业橡胶硫化促进剂、纤维脂肪涂层稳定剂、双氧水稳定剂和合成樟脑。

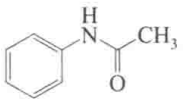
乙酰苯胺属于非甾体抗炎药，通常这类药物的作用靶点为环氧合酶和脂氧合酶。**彩插 1** 给出了乙酰苯胺和环氧合酶-2（COX-2）可能的结合方式模型，蛋白晶体结构为 PDB：5F1A，分子模拟结果显示乙酰苯胺可以与水杨酸结合位点形成良好的相互作用。乙酰苯胺在此位点的作用模式以及结合口袋的表面图分别如**彩插 1**（A）、（B）所示。（乙酰苯胺中乙酰基部分的羰基氧与 Ser 530 侧链的羟基形成氢键，苯环与周围的氨基酸形成疏水作用）

Ⅰ 目的与要求

1. 掌握重结晶原理。
2. 掌握重结晶操作。
3. 了解乙酰苯胺与靶标的作用方式。

Ⅱ 实验原理

1. 主要反应物和产物的物理常数

名称	结构式 /CAS号	分子式 /分子量	沸点或熔点 /℃	溶解度/(g/L)
乙酰苯胺	 103-84-4	C_8H_9NO 135.16	m.p. 113～115	水:55 (100 ℃),4.6 (20 ℃); 乙醇:36.9 (20 ℃); 甲醇:69.5 (20 ℃); 氯仿:3.6 (20 ℃)

2. 重结晶原理

反应获得的化合物往往含有一些杂质，这些杂质可以是可溶的，不易溶解的和有色的化合物。若要获得纯净的化合物，必须除去以上所述及的杂质。重结晶是除去固体化合物杂质的常用方法之一。

重结晶的原理是：一般情况下，溶质在溶液中的溶解度随着温度的升高而增大。例如，图 1-2 给出了乙酰苯胺在水中的溶解度曲线，在水中，乙酰苯胺随着温度的升高其溶解度也逐渐升高，当温度从 20 ℃升高到 100 ℃时，溶解度则从 4.6 g/L 增大至 55 g/L。

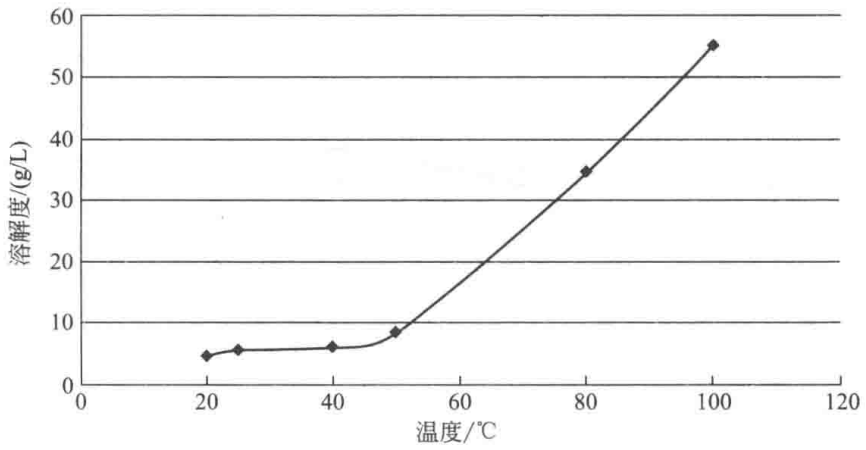


图 1-2　乙酰苯胺在水中的溶解度曲线

图 1-3 为重结晶操作的一般过程。首先，选择适宜的重结晶溶剂，使含有杂质的固体化合物溶于溶剂或者在接近沸点时溶于溶剂，然后，通过热过滤除去不溶性杂质。热过滤过程中要先将过滤装置预热以防止过早析出晶体而无法过滤。随后，在热的滤液逐渐冷却的过程中，重结晶后析出纯的晶体，过滤收集纯化后的产物，而可溶性杂质留在滤液中。

重结晶溶剂的选取是非常重要的因素。常用的重结晶溶剂的沸点和介电常数汇总于表 1-1。