PRACTICAL MEDICINAL CHEMISTRY

Dr. Rajashree S. Chavan Dr. H. N. More Ms. Smita J. Pawar Dr. Sanjay D. Sawant





NIRALI PRAKASHAN

PRACTICAL MEDICINAL CHEMISTRY

[For Third / Final Year B.Pharm]

Dr. Mrs. RAJASHREE SUNIL CHAVAN

Associate Professor in Pharmaceutical Chemistry, Seth Govind Raghunath Sable College of Pharmacy, SASWAD - 412301 (Maharashtra).

Dr. H. N. MORE

Principal and Professor in Pharm. Chemistry, Bharati Vidyapeeth College of Pharmacy **KOLHAPUR**.

Ms. SMITA JAGANNATH PAWAR

Associate Professor in Pharm. Chemistry, Seth Govind Raghunath Sable College of Pharmacy, SASWAD - 412301 (Maharashtra).

Dr. S. D. SAWANT

Principal and Professor in Pharm. Chemistry STES's Smt. Kashibai Navle College of Pharmacy Kondhwa. **PUNE.**

Price ₹ 120.00



N1654

Practical Medicinal Chemistry

ISBN 978-93-83525-10-2

Fifth Edition : June 2018 © : Authors

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Published By:
NIRALI PRAKASHAN

Printed By : YOGIRAJ PRINTERS AND BINDERS

Abhyudaya Pragati, 1312, Shivaji Nagar, Off J.M. Road, PUNE – 411005 Works: Sr. No. 10\1,Ghule Industrial Estate, Nanded Village Road,

Tel - (020) 25512336/37/39, Fax - (020) 25511379 Email : niralipune@pragationline.com TAL-HAVELI, DIT-PUNE 411041. Mobile - 9850046517, 9404225254

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Preface ...

The subject **Medicinal Chemistry** is at the heart of modern drug discovery and development. One of the important steps in the process of drug discovery is synthesis of pure drug molecules through most efficient, less time consuming, economical and environment friendly route, which is an intricate and most challenging task for the medicinal & organic chemists. The medicinal chemists are primarily concerned with synthesis of organic molecules to be used as pharmaceuticals and the way these molecules interact in biological pathways. The synthesis involves a careful selection of a particular type of reaction, reagents, solvents, catalysts along with optimized reaction conditions.

An understanding of organic reaction mechanism is essential otherwise, it is impossible to plan organic synthesis. The publication of this book is undertaken with a primary aim is to provide information to the undergraduate students regarding synthesis of different organic compounds of medicinal importance in pharmaceutical chemistry. Our focus is not only on the aspects relevant to the synthesis and characterisation of compounds but also on principles and reaction mechanisms involved in a particular synthesis. The contents of this book are divided into two sections. Section-A provides the concise information on various laboratory techniques used for isolation, purification and synthesis of organic compounds. It also describes methods used for identification and characterisation of synthesised compounds. Section-B deals with the discussion of the procedure along with the mechanism of the reactions of some organic compounds. Appendix includes glossary which explains the significant terms and concepts relevant to the subject, table of physical constants and bibliography. This has been our first attempt to fulfill the needs of undergraduate students of medicinal chemistry practical course of reputed Universities.

We express our sincere thanks to parent society of our college 'Pune District Education Associations' Pune, and its office bearers for their motivation.

We are thankful to Dr. Ashok Bhosale, Principal, PDEA's Seth Govind Raghunath Sable College of Pharmacy, Saswad for his valuable cooperation and encouragement. We are thankful to Mr. S. B. Gokhale for his constant criticism and timely guidance. We would like to mention our special thanks to Mr. Dineshbhai K. Furia, Mr. Jignesh Furia, Mr. Malik Shaikh, Mr. Ashok Bodke and other staff of Nirali Prakashan, Pune. We would like to express our heartfelt thanks to everyone who directly or indirectly helped us in compilation of this book. We are indebted to our family members for their love and support which is our great strength.

All comments and suggestions will be received with gratitude.

Contents ...

24. Synthesis of Cyclohexanone

SECTION - A I.1 - I.1 0. Instructions to the students 1. First Aid Treatment 1.1 - 1.22.1 - 2.22. Care in Chemistry Laboratory 3. Isolation and Purification of organic compounds 3.1 - 3.104.1 - 4.34. Characterization of the compounds SECTION - B SYNTHESIS OF ORGANIC COMPOUNDS OF MEDICINAL IMPORTANCE Synthesis of Anthranilic acid 1.1 - 1.32.1 - 2.22. Synthesis of 9,10- Anthraquinone 3. Synthesis of Antipyrine (3-methyl-1-phenylpyrazol-5-one) 3.1 - 3.24.1 - 4.24. Synthesis of Acetanilide 5.1 - 5.25. Synthesis of Aspirin 6.1 - 6.26. Synthesis of Acetophenone 7. Synthesis of Benzimidazole 7.1 - 7.28. Synthesis of 2-Methyl Benztriazole 8.1 - 8.29. Synthesis of Benzil Alcohol 9.1 - 9.210. Synthesis of Bnzstriazole 10.1 - 10.111. Synthesis of Benzil 11.1 - 11.2 12. Synthesis of Benzilic Acid 12.1 - 12.2 13. Synthesis of Benzophenone oxime 13.1 - 13.214. Synthesis of Benzanilide 14.1 - 14.2 15.1 – 15.2 15. Synthesis of Benzocaine 16. Synthesis of Barbituric Acid 16.1 - 16.2 17. Synthesis of Benzoic Acid 17.1 - 17.2 18. Synthesis of Benzhydrol 18.1 - 18.219. Synthesis of Caprolactum 19.1 - 19.2 20. Synthesis of Cinnamic acid 20.1 - 20.321. Synthesis of Chloramine-T 21.1 - 21.222. Synthesis of Dibenzalacetone 22.1 - 22.323. Synthesis of *p*-Nitroacetanilide 23.1 - 23.2

24.1 - 24.2

25.	Synthesis of Diazoaminobenzene	25.1 – 25.2
26.	Synthesis of Ethyl Nicotinate	26.1 - 26.2
27.	Synthesis of Ethyl Benzene	27.1 – 27.2
28.	Synthesis of Ethyl Benzoate	28.1 - 28.2
29.	Synthesis of Methyl Orange	29.1 - 29.3
30.	Synthesis of Methyl Red	30.1 - 30.3
31.	Synthesis of Methyl Salicylate	31.1 - 31.2
32.	Synthesis of 1-Naphthalene	32.1 – 32.2
33.	Synthesis of <i>p</i> -Nitroaniline	33.1 – 33.2
34.	Synthesis of <i>p</i> -Nitrophenol	34.1 - 34.2
35.	Synthesis of <i>o</i> -lodobenzoic Acid	35.1 – 35.2
36.	Synthesis of 2-Phenylindone	36.1 - 36.3
37.	Synthesis of <i>p</i> -Toluene Sulphonamide	37.1 - 37.1
38.	Synthesis of 2, 5-Dihydroxy Acetophenone	38.1 - 38.2
39.	Synthesis of Propyl Benzene	39.1 – 39.2
40.	Synthesis of 4-Fluoroacetophenone	40.1 - 40.2
41.	Synthesis of Phthalimide	41.1 - 41.2
42.	Synthesis of Phenytoin	42.1 – 42.2
43.	Synthesis of Thiobarbituric Acid	43.1 – 43.2
44.	Synthesis of 2-Naphthyl Benzoate	44.1 – 44.2
45.	Synthesis of 3, 5-Dicarboxylate-2, 6-Dimethyl Pyridine	45.1 – 45.2
46.	Synthesis of <i>p</i> -Acetamidobenzenesulphonyl Chloride	46.1 - 46.2
47.	Synthesis of <i>p</i> -Acetamidonenzenesulphonamide	47.1 – 47.2
48.	Synthesis of Sulfaniliamide (p-Aminobenzenesulfonamide)	48.1 – 48.2
49.	Synthesis of Isonicotinic Acid	49.1 – 49.2
50.	Synthesis of 4-Methyl-7-Hydroxycoumarin	50.1 - 50.2
•	Glossary	G.1 – G.2
•	Table of Physical Constants	T.1 – T.2
•	Index	I.1 – I.1
•	Bibliography	B.1 – B.1



INSTRUCTIONS FOR STUDENTS

- 1. Students should note the following essential requirements for pharmaceutical medicinal chemistry practical: **Observation note book/journal, white apron, match box, soap, napkin, spatula, calculator**, etc.
- 2. Before commencing work, make sure of what is to be done and how it is to be done.
- 3. Listen carefully to the instructions given by teacher about importance of subject, graphical structure, skills to be developed; information about equipment, instruments, procedure, and method of continuous assessment, tentative plan of work in laboratory and total amount of work to be done in a year.
- 4. Student shall clear all his/her doubts before starting the practical.
- 5. Students shall undergo study visit of the laboratory for types of equipment, instruments, material to be used, before performing experiments.
- 6. Read the write up of each experiment to be performed a day in advance.
- 7. Organise the work and arrange the experiment by issuing required apparatus and chemicals.
- 8. Follow the management and complete all experiments on time.
- 9. Understand the purpose of experiment and its practical implications.
- 10. Student shall refer to the practical handbook for organic chemistry for systematic qualitative analysis of unknown organic compound.
- 11. Student should maintain discipline in the laboratory. Any misbehaviour or indiscipline in the laboratory may lead to serious mishap.
- 12. Students should handle hazardous chemicals carefully. They should wear hand gloves while handling corrosive chemicals like bromine, conc. Sulphuric acid, conc. Nitric acid etc.
- 13. Students shall wash their hands thoroughly with soap, before leaving laboratory.
- 14. Student should not hesitate to ask for help in case of any difficulty faced during conduct of practical.
- 15. Student should develop the habit of not to being totally dependent on teachers but to develop self-learning techniques by referring to library resources.
- 16. Students should develop the habit of interacting with the teacher without hesitation with respect to the academics involved.
- 17. Students should be well prepared while submitting the write up of the exercise.
- 18. Do not use cell phones in the laboratory.

1

FIRST AID TREATMENT

(A) Burns

1. Burns caused by dry heat (e.g. by flames, hot objects etc.):

For slight burns in which the skin is not burnt, apply Burnol. Call for medical aid for more severe burns.

2. Acid on the skin:

Wash immediately and thoroughly with liberal quantity of water, then with saturated sodium bicarbonate solution and finally with water.

3. Alkali on the skin:

Wash immediately with a large volume of water, then with 1% acetic acid and finally with water.

4. Bromine on the skin (Serious):

Wash the affected part immediately with cloth/cotton sponge soaked in light petroleum and then rub glycerine well into the skin. After a little while, remove the superficial glycerine and apply Burnol.

5. Sodium on the skin:

If any small fragment of sodium can still be seen, remove it carefully with forceps. Wash thoroughly with water, then with 1% acetic acid and finally with water.

6. Organic substances on the skin:

Wash with cotton/cloth soaked in rectified spirit, then with soap and warm water.

(B) Cuts:

If the cut is only a minor one, allow it to bleed for a few seconds, make sure that no glass particles remain. Apply a disinfectant (rectified spirit or Dettol) and bandage. For serious cuts, send for a doctor at once, meanwhile, wash with disinfectant and check bleeding by applying pressure immediately above the cut. Continuous pressure should not be maintained for more than five minutes.

(C) Eye Accidents:

In all cases, the patient must see a doctor. If the accident appears serious, patient should be summoned immediately while first aid is applied.

1. Acid in the eye, if the acid is dilute:

Wash the eye repeatedly with 1% sodium bicarbonate solution in the eye cup.

If the acid is concentrated,

First wash the eye with a large amount of water and then continue with the bicarbonate solution.

2. Caustic alkali in the eye (Serious)

Proceed as for acid in the eyes, but wash with 1% boric acid solution in place of bicarbonate solution. Do not neglect. Consult a physician.

3. Bromine in the eye (Serious)

Wash thoroughly with water and the immediately with 1% sodium bicarbonate solution.

4. Glass in the eye

Remove lose glass very gently with forceps or by washing with water in an eye cup. Call for a doctor immediately.

(D) Fire

Inflammable solvents should be handled carefully.

- 1. Carbon tetrachloride should not be used if sodium or potassium is present as violent explosions may result.
- 2. The laboratory must be well ventilated immediately.
- 3. For burns of oil or organic solvents, do not use water as it will spread the fire. Mixture of sand and sodium bicarbonate is very effective. Dry powder extinguisher is available in almost all the laboratories.

(E) Poisons

Solids or liquids

- 1. If it is taken in the mouth but not swallowed the spit out at once and wash repeatedly with water.
- 2. If swallowed: Call a doctor immediately. In the meanwhile, give an antidote according to the nature of the poison.
 - **(A) Acid (including oxalic acid):** Dilute by drinking a large amount of water, followed by lime water or milk of magnesia.
 - **(B) Caustic alkalis:** Dilute by drinking much water, followed by vinegar, lemon or orange juice, or solution of lactic acid or citric acid. Milk may then be given but no emetics.
 - (C) Salts of mercury compound: Give milk of egg.
 - **(D) Arsenic of mercury compound:** Give an emetic immediately, e.g. one teaspoonful or mustard, or one teaspoonful of salt or zinc sulphate, in a cup of warm water.
 - **(E) Gas:** Remove the victim to the open air and loosen clothing at the neck. To counteract chlorine or bromine fumes if inhaled in only small amounts, inhale ammonia vapour or gargle with sodium bicarbonate solution. Afterwards, the patient should suck eucalyptus oil soaked cotton swabs or drink warm dilute peppermint or cinnamon essence to soothe the throat and lungs. If breathing has stopped, apply artificial respiration, call medical aid immediately.



CARE IN CHEMISTRY LABORATORY

- > Benches should always be kept clean and tidy. All the spillages of both solids and liquids must be cleared away immediately.
- All glassware must be scrupulously cleaned.
- ➤ Under no circumstances should be working surface of bench become cluttered with apparatus.
- All apparatus associated with one particular operation should be grouped together on the bench.
- If a solution, precipitate, filtrate, etc, is set aside for subsequent use, the container must be labeled so that contents can be readily identified.
- > Reagent bottles must be replaced on the reagent shelves immediately after use.
- Normal practice is that all determinations are performed in duplicate.
- A stiff covered notebook of A 4 size must be provide for recording experimental observations as they made.
- Fire extinguisher must be placed handy in every chemical laboratory.

SAFETY

Safety in the laboratory is essential at all times. You are responsible for the safety of any other person as well as your own. Many chemicals encountered in analysis are poisonous and must be carefully handled. More precaution is to be taken for concentrated acids, poisons such as potassium cyanide, halogenated solvents, benzene, and mercury.

Many operations involving chemical reactions are potentially dangerous and recommended procedures must be followed and obeyed. All laboratory workers/person should familiarise themselves with local safety requirements, which may include the compulsory wearing of lab coats and safety spectacles, and the positions of first aid equipment.

GRADES AND PROPERTIES OF CHEMICALS

In the analytical chemistry, accuracy of analysis is affected by quality of the regents. The chemicals, which are used in the laboratory for chemicals analysis, are available in different grades as follows.

1. **Technical or commercial grade:** These are used when the high purity is not required e.g. preparation of cleaning solution. For this are used potassium dichromate and sulphuric acid.

- **2.** Chemically pure (cp grade): These are more refined than the technical grade. These chemicals are not suitable for analytical work or if, to be used, then they must be tested.
- **3. L.R. grade:** These are used for analytical work. Its label indicates maximum limits of impurities allowed by the specifications, or actual results of analysis for various impurities.
- **4. Primary standard:** These are in the purest form, carefully analysed and the assay value (percentage purity) is printed on the label.
- **5. Pharmacopoeial grade chemicals:** These chemicals confirm the tolerances set by pharmacopoeias. (Ex. Indian pharmacopoeia and British Pharmacopoeia).

PRECAUTIONS IN HANDLING CHEMICALS

Handling of chemicals, especially hazardous chemicals must be done with due care. Routine lab work must follow certain rules while handling the chemicals.

- Select the required grade of the chemical for the analytical work.
- Select the smallest pack available.
- Replace the top of every container immediately after removal of reagent; do not rely on someone to do this.
- Use a clean spatula for removing the reagent from the container. Follow the special instructions, if any mentioned on the container.
- Remove the required amount of chemical reagent from the container, so you need not to return the excess amount to container, thus avoiding the contamination of the reagent.
- Keep the reagent and the laboratory balances clean. Clean any spilt chemicals immediately.
- While handling hazardous or toxic chemicals use hand gloves and mouth mask.



ISOLATION AND PURIFICATION OF COMPOUNDS

Isolation of pure compounds from its source consists of three steps:

- 1. Isolation
- 2. Purification
- 3. Test of purity

Isolation of an organic compound from its source (plants, animals, coal tar, petroleum etc.) means its separation or extraction in crude form containing many other substances. Dialysis, diffusion, ultracentrifugation, electrophoresis are the modern processes commonly used for isolation.

The substances which contaminate a desired compound are called impurities. The process of removal of impurities from the desired compound is called purification. Without purification, no compound can be subjected into structural elucidation.

Substances in the solid form are mainly of two types-crystalline and amorphous. A crystalline substance has a definite geometrical shape. In crystals, there is a regular arrangement of atomic, ionic or molecular constituents. Thus, there is long range regularity in the internal structure. For example, sodium chloride crystals are cubical; alum crystals are octahedral while copper sulphates are prismatic.

Organic substances like acetanilide, citric acid, phthalic acid, benzoic acid etc. are crystalline. Crystalline substances have a definite and sharp melting point.

Criteria of purity:

After isolation of a pure substance, it is essential to confirm its purity. A chemically pure compound has specific physical properties such as crystalline form, refractive index, melting point, boiling point etc. In ordinary laboratory work, the melting point of a solid and boiling point of liquid are generally considered as sufficient indication of the purity of a compound. An impure compound (solid) melts slowly over many degrees while an impure compound (liquid) boils slowly over several degrees.

The methods of purifications are

- 1. Liquid liquid extraction
- 2. Chromatographic separation
- 3. Recrystallization
- 4. Sublimation
- 5. Distillation at atmospheric pressure
- 6. Distillation at reduced pressure
- 7. Steam distillation

FILTRATION

Filtration by means of suction is employed, when possible, as this gives a more rapid and complete separation of mother liquid from substance. Most of times any funnel can be made to work if equipped with a platform on which the filter paper can be laid. Such a platform can be made from a small ceramic plate with many small holes drilled through it or wire mesh. As long as the platform does not react with your substance, it should be acceptable. Buchner funnels come with perforated discs and are inexpensive. Some things to remember during vacuum (suction) filtration are: the funnel tip should be below the vacuum source outlet, cut your filter paper to fit the funnel platform exactly, in other words, do not let the paper rest on the sides of funnel.

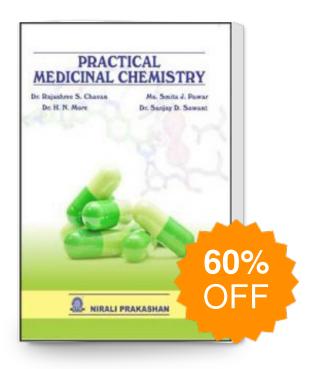
GRAVITY OR SIMPLE FILTRATION

This is the most common method of filtration and is used to remove an insoluble solid material from a solution. The solid could be the required product or an impurity or an additive such as a drying agent. A filter paper is folded (conventional or fluted) and placed in a filter funnel which is then placed in the neck of an Erlenmeyer flask or supported in a clamp or ring stand. The solution to be filtered is then slowly and carefully poured into the funnel taking care not to fill the funnel above the edge of the filter paper.

HOT FILTRATION

Sometimes during a gravity filtration, crystals can start to grow in the filter funnel. This problem can be avoided by using a hot filtration where the filtration apparatus is heated in order to prevent the solution from cooling significantly. The hot filtration process is best carried out using a fluted filter paper and a stemless filter funnel. Support the stemless filter funnel on an iron ring clamp if it is at all insecure. If pressure builds up in the flask due to the presence of hot vapours, the filtering action will slow down; use of the fluted paper reduces this. The hot solution should be filtered quickly through the fluted paper in a stemless filter funnel into an Erlenmeyer flask. A small piece of wire or paper may be inserted between funnel and Erlenmeyer to prevent formation of a seal and subsequent pressure build-up. If crystals start to form in the paper or in the filter funnel, then the Erlenmeyer containing a few drops of pure solvent with the funnel and paper in place should be heated on a steam bath and the entire filtration procedure carried out on the steam bath. Hot solvent may be added to remove any crystals appearing on the filter paper.

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Publisher: Nirali Prakashan ISBN: 9789383525102

Author: Dr. Mrs. Rajashree Sunil Chavan, Ms. Smita Jagannath Pawar, Dr. H. N. More, Dr. S. D Sawant

Type the URL: http://www.kopykitab.com/product/20519



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