Designing Organic Syntheses

A Programmed Introduction to the Synthon Approach

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PREFACE

There are some excellent books written about organic synthesis but they mostly present complete syntheses of complicated molecules. They translate from the language of synthesis into that of organic chemistry. I have tried in this book to teach people to speak the language of synthesis themselves, using the grammar of synthon and disconnection. The programme was originally written for second year university students and re-written after they had used it.

I thank Drs. Ian Fleming, Ted McDonald, Jim Staunton, and Peter Sykes, and the IB advanced chemists of 1976-7 for their perceptive comments, Dr. Denis Marrian for his enthusiastic help in converting the original sketches into a book, and Miss Lesley Rolph for typing the printed words.

Cambridge 1977 Stuart Warren

NOTE FOR INSTRUCTORS

The programme aims to allow students to teach themselves but it shouldn't mean any less work for you. Because the students discover what they don't know, they should have more sensible questions to ask you than if they were reading a textbook or revising from their notes. My aim is to give you more time for real teaching. The programme should do the ground work and you should be able to set suitable problems and discuss then profitably. The programme itself has plenty of problems of this sort (see review and revision problems, and those at the end without worked solutions), and the source books below will give you hundreds more. The literature references are so that you can look up details if you are asked - I imagine few students will use them.

Source Books:

N. Anand, J.S. Bindra, and S. Ranganathan,
'Art in Organic Synthesis',
Holden Day, San Francisco, 1970.

J. ApSimon (editor),
'The Total Synthesis of Natural Products',
Wiley, New York, 1973, 3 Volumes.

K. Nakanishi et al.,
'Natural Products Chemistry',
Academic Press, New York, 1974, 2 Volumes.

British Pharmacopoeia Commission,
'Approved Names 1973',
HMSO, London, 1973, and later supplements.

CONTENTS

WHAT DO YOU NEED TO KNOW BEFORE YOU START?

Though the programme may introduce you to some new reactions, its main aim is to suggest an analytical approach to the design of syntheses. You therefore need to have a reasonable grounding in organic chemistry so that you are familiar with most basic organic reactions and can draw out their mechanisms. If you are a third year university student, a graduate, or someone with experience of organic chemistry in practice you will probably be able to work straight through the programme to learn the approach and not need to learn any new material. If you are a second year university student or someone with a limited knowledge of organic reactions you may find you need to learn some reactions as you go along. I have given references to these books to help you:

'The Carbonyl Programme':
"Chemistry of the Carbonyl Group, A Programmed Approach to Organic Reaction Mechanisms", Stuart Warren, Wiley 1974. This programme leads up to the present one.

'Fleming':
"Selected Organic Syntheses", Ian Fleming, Wiley 1973. Synthesis from the other side: notable examples of organic syntheses carefully explained in detail.

'Tedder':
"Basic Organic Chemistry", J. M. Tedder, A. Nechvatal, and others, Wiley, 5 volumes 1966-1976. A complete textbook of organic chemistry. Explains all the reactions used in the programme and describes many syntheses in detail.

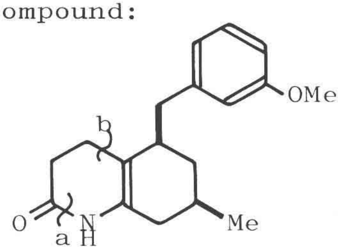
'Norman':
"Principles of Organic Synthesis", R. O. C. Norman, Methuen, 1968: A textbook of organic chemistry from the point of view of synthesis. An excellent source book for all the reactions used in this programme.

Whoever you are, you will certainly find discussion with your fellow students one way to get the most out of the programme and you may well find it is a good idea to work on the more difficult problems together. The review problems, revision problems, and problems without worked solutions are ideal for this. In some cases I have given references to the original literature so that you can find out more details of the various possible approaches for yourself if you want to. It isn't necessary to look up any of these references as you work through the programme.

The point of programmed learning is that you learn at your own pace and that you yourself check on your own progress. I shall give you information and ideas in chunks called frames, each numbered and separated by a black line. Most frames contain a question, sometimes followed by a comment or clue, and always by the answer. You must WRITE DOWN on a piece of paper your answer to each question. You'll find that you discover as you do so whether you really see what is being explained or not. If you simply say to yourself 'Oh, I can do that, I don't need to write it down', and look at the answers, you're missing the opportunity to check on your own progress as well as probably deceiving yourself.

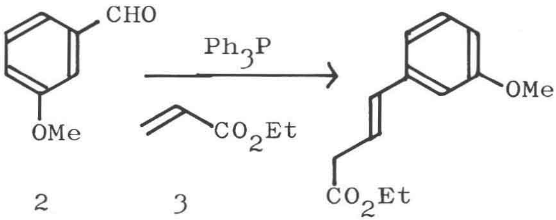
When you are ready to start, cover the first page with a card and pull it down to reveal the first frame. Read and act on that frame, then reveal frame 2 and so on. If you are unfamiliar with the disconnection approach, I suggest you read the introduction 'Why bother with disconnections' so that you can see what I'm driving at. Otherwise the first sections of the programme may seem rather pointless.

The aim of this programme is that you should learn how to design an organic synthesis for yourself. Supposing you wanted to make this compound:



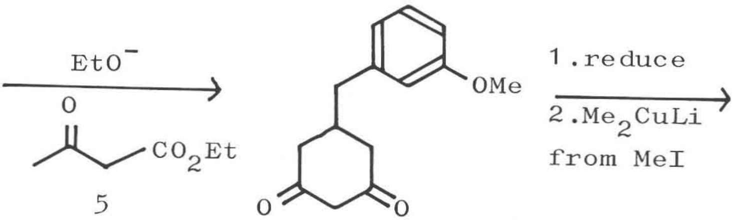
(1)

You would find that it had already been made by the route outlined on the chart on the next page. You could then buy the starting materials (compounds 2, 3, 5, 8, and MeI) and set to work. But supposing 1 had never been synthesised. How would you design a synthesis for it? You don't know the starting materials - all you know is the structure of the molecule you want - the TARGET MOLECULE. Obviously you have to start with this structure and work backwards. The key to the problem is the FUNCTIONAL GROUPS in the target molecule, in this case the nitrogen atom, the carbonyl group, the double bond and the benzene ring with its methoxyl group. You should learn from the programme that for most functional groups there are one or more good DISCONNECTIONS - that is imaginary processes, the reverse of real chemical reactions, which break a bond in the target molecule to give us the structure of a new compound from which the target molecule can be made.


CHO
Ph3P
OMe
CO2Et
OMe
CO2Et

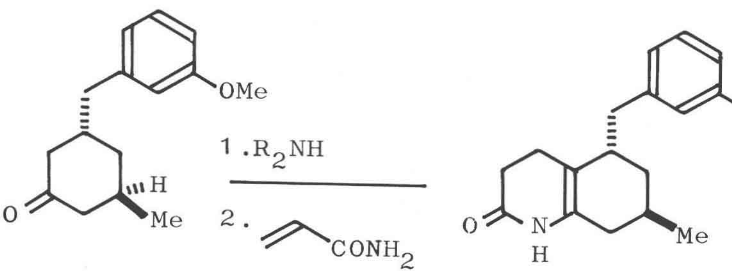
2 3

4

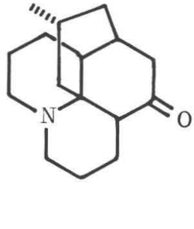

EtO-
O
CO2Et
OMe
1.reduce
2.Me2CuLi
from MeI
O
O

5

6

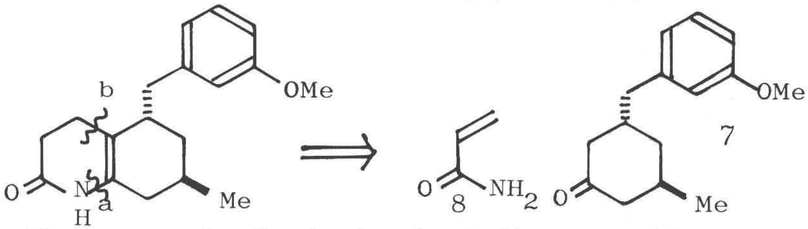

OMe
H
Me
O
1.R2NH
2.
CONH2
O
N
H
Me

7 8 1


N
O

9

Here the first disconnection (a) was of a C-N bond, the second (b) of a C-C bond taking us back to compounds (7) and (8):



8 7

These are in fact standard disconnections which you will meet in sections G and C of the programme. The first part of the programme (Sections B to H) shows you how to use disconnections and which disconnections are good ones. The second part shows you how to choose between alternative series of disconnections to get good synthetic schemes.

When you have finished the programme you should be able to design syntheses for molecules of the complexity of (1). Given this problem, you might not come up with the solution shown in the chart because there is no single "right answer" to a synthesis problem - any given molecule may well be made successfully by several different routes. In practice each of your proposals would have to be tested in the lab., and your overall scheme modified as a result. There were in fact several changes of plan in the synthesis of (1) and you can read more about the details in Stork's article in Pure and Applied Chemistry, (1968, 17, 383) where you will see that he used (1) as an intermediate in the synthesis of the alkaloid lycopodine (9). That is a target molecule beyond the scope of this programme, but organic chemists plan such syntheses using the same principles as you will learn here. You must first start at the beginning and learn in Section A how to use simple disconnections.