GENERAL METHODS FOR THE CONSTRUCTION OF COMPLEX MOLECULES

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This paper deals with the subject of synthetic methodology at two very different levels, and accordingly, it is divided into two parts. The first is concerned mainly with the general methods by which the plan of a synthesis is derived, and the second part places emphasis on the operations which constitute the individual steps of a synthesis and on some specific recent developments in this field.

PART I

GENERAL PRINCIPLES FOR THE FORMULATION OF A SYNTHETIC PLAN

The achievement of a synthesis of a complex organic molecule involves a number of distinctly identifiable operations which, however, are not strictly independent of one another. These include the choice of the molecule to be synthesized, the development of a synthetic strategy and plan in general outline, the selection of specific individual steps and their ordering, and the experimental execution of the synthesis. The absence of a clean separation between component elements makes the task of analysing and understanding Synthesis as an intellectual discipline appear quite forbidding, especially in the most crucial aspect, derivation of a general plan. Further, the enormous diversity and number of organic structures now known to exist, the incredibly broad spectrum of reactions available for synthesis, and the uncertain and severe limits on the applicability of any given reaction all combine to create an impression that the design of a synthesis is apt to be tenuously hypothetical and is mainly a function of the unique circumstances in each particular case and, moreover, that considerations of a highly general nature are neither dominant nor very useful. None the less, a sufficiently great number and variety of syntheses have now been completed to encourage attempts at setting down in a generalized form the process by which a synthetic chemist devises an original but valid synthetic route to a complicated structure. Such an effort surely is more than an intriguing theoretical exercise; it is a prerequisite to a deeper comprehension of Synthesis and the methodologies which are fundamental to it, and it is likely to be a keystone in the rational development of Synthesis to still higher forms. For example, any technique for the automatic generation of synthetic schemes by a computer will require a complete and detailed definition of the elements of Synthesis and their mutual interaction, in a most general sense.

Axioms

There are certain considerations which can be regarded as axiomatic to Synthesis and which serve as pre-conditions for any general analysis of methodology. These include the following:

1. The various elements involved in the solution (and even the selection!) of a synthetic problem are not separable. If a division of these elements in Synthesis is made for purposes of simplifying an analysis, it must be compensated for by allowing their interaction at some stage to produce further modification of the process.

2. A very large number of possible routes to the synthesis of a complex molecule can usually be generated. Each of these involves a sequence of reactions and proceeds via a number of intermediates whose synthesis is more direct than that of the target molecule. Naturally, the starting point for any route should be a readily available synthetic substance.

3. These possible routes are derivable by the recognition of structural units within molecules which can be formed and/or assembled by known or conceivable synthetic operations. (In the discussion which follows, these units are designated as "synthons". In this paper the term "synthetic operations" is used in the molecular sense to denote structural transformations rather than in the laboratory sense, which would imply manipulation.)

4. There are definite but not absolute criteria by which the merits or quality of alternative projected syntheses can be judged. Often there are a sufficiently large number of unknowns to render the selection of a superior synthetic route arbitrary. These criteria, none the less, always serve the very important purpose of dictating the rejection of a very large number of inferior possibilities.

5. The specific criteria by which synthetic alternatives may be judged are on the whole elementary to the organic chemist. The items which follow are important and indicative.

   A. The probability of achieving the desired change at each step in the sequence should be high. This implies that at each step the possibility of competing reaction paths should be minimized and that certain controls may have to be introduced in a synthesis to prevent undesired reactions and to position and to orient newly introduced units. The effect of these conditions will be to insure high efficiency in the conversion of input substances to end product.

   B. Bypass routes or potential alternatives should exist, particularly where the functioning of one or more of the individual steps is questionable.

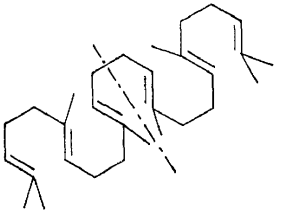
   C. The solution should be simple. This implies the desirability of a maximum correlation between the individual synthetic operations so that each one permits, assists, or simplifies the others in some way. The absence of correctional steps is also implied.

6. If possible, the chemical operations which constitute the individual steps of a synthetic sequence should be chosen from known chemical reactions for which there is a reasonable understanding of mechanism and of scope. However, it may be desirable to attempt a synthesis by the use of new reactions if a great simplification can result or if there is simply no alternative

7. Syntheses which can be carried out simply by analogy with closely related known cases are not considered in the category of synthesis under discussion. The synthesis of a new, but simple, indole by a standard method, such as the Fischer synthesis, exemplifies this type of simple synthesis.

Simplification

Given a complex molecule which is to serve as a target for synthesis, the first step clearly is to attempt a simplification of the problem. Here the analysis of actual or *potential* molecular symmetry can be of importance. The synthesis of squalene (I) is simplified by the fact that the molecule contains two identical C_{15} units joined symmetrically by a central carbon–carbon bond. Another example of this type of simplification is the synthesis



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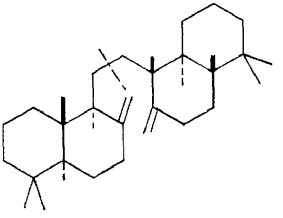

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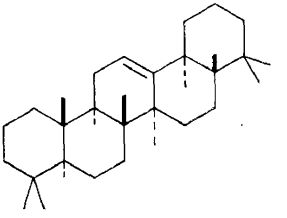
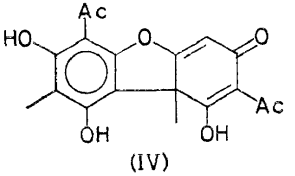


(II)

of the complex alkaloid, C-toxiferine I, from the Wieland–Gumlich aldehyde[1]. In the case of the synthesis γ-onocerane (pentacyclosqualene) (II), the task can be facilitated by the recognition of a synthetic route via the symmetrical intermediate (III); in this case the simplification is less obvious[2]. A slightly different and even more subtle illustration of simplification using symmetry considerations is Barton's synthesis of usnic acid (IV), a molecule which itself appears totally devoid of symmetry but which can be synthesized in one operation by the unsymmetrical coupling of two phenoxy radicals, each derived from the same phenol (V)[3]. These radicals can be formulated as (VI) and (VII). In general, a molecule may be said to possess *potential* symmetry when it can be disconnected to give a symmetrical structure or two or more synthetically equivalent structures.



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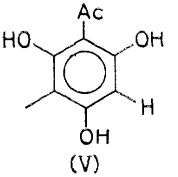

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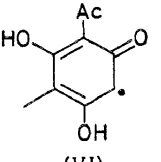

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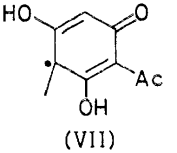


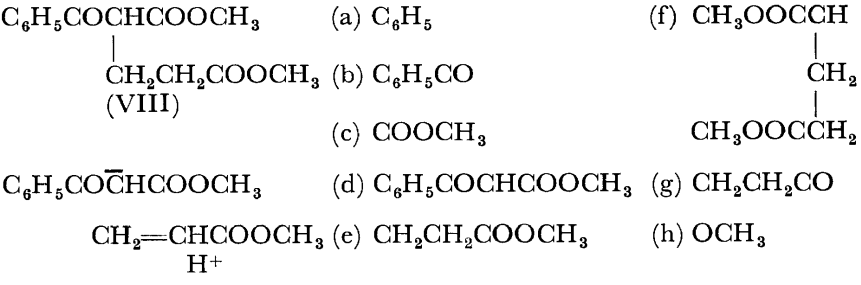
(VII)

Here a most important point must be made: even in the earliest stages of the process of simplification of a synthetic problem, the chemist must make

use of a particular form of analysis which depends on the interplay between structural features that exist in the target molecule and the types of reactions or synthetic operations available from organic chemistry for the modification or assemblage of structural units. The synthetic chemist has learned by experience to recognize within a target molecule certain units which can be synthesized, modified, or joined by known or conceivable synthetic operations. Thus, with the knowledge of the coupling reactions of phenoxy radicals, enolization reactions, Michael-type addition reactions, and 1,2-elimination reactions, two synthetic units can be recognized within the usnic acid structure which are related to the fragments (VI) and (VII) and, therefore, to the precursor (V).

It is convenient to have a term for such units; the term "synthon" is suggested. These are defined as structural units within a molecule which are related to possible synthetic operations (and, therefore, to the reverse operations of degradation). A synthon may be almost as large as the molecule or as small as a single hydrogen; the same atoms within a molecule may be constituents of several overlapping synthons. Thus, for the molecule (VIII) many synthons can be recognized, including a–h. The units (d) and (e) are valid synthons, since they may be joined by a known synthetic operation, Michael addition (after minor modification to $C_6H_5CO\bar{C}HCOOCH_3$ and $CH_2{=}CH{-}COOCH_3 + H^+$)

SYNTHONS



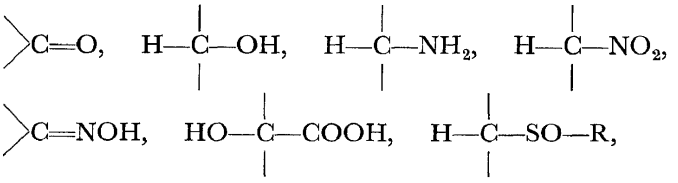
In general, the greater the number and variety of synthons which can be defined, the greater will be the complexity of the synthetic problem. Further, recognition of some synthons (usually the larger or major synthons) normally is more useful in analysis than that of others. The greater the degree of connectivity within a molecule (*e.g.*, the larger the number of rings), the greater the number of possible synthons. In principle there is no reason why the number of derivable synthons cannot exceed the number of atoms in a molecule rich in internal connection.

The recognition of synthons within molecules is purely a utilitarian device; the derivation of all the possible synthons in a molecule may never be required. On the other hand, the consideration of a molecule as a collection of the constituent atoms is perfectly definite, but hardly useful in the design of a synthesis.

The beginning student of organic chemistry, when asked to devise a synthesis, such as the formation of butane-1,3-diol from a 2-carbon precursor, often does not appreciate the beauty of the problem, at least in part because

he has generally not been instructed in the simple but fundamental recognition process on which is based all synthetic design, from the simplest to the most complex.

A functional group may be regarded as a synthon, and it is helpful to consider sets of equivalent synthons, *e.g.*,

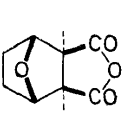


which may be interconvertible by synthetic operations. In some cases a synthetic problem is simplified by replacing one or more synthons by equivalent ones. Clearly, this procedure can also lead to a reduction in the number of functional groups: for example, one C=C might replace two carbonyl groups.

The *next* stage of the simplification process often derives from a consideration of the three-dimensional character (*i.e.*, stereostructure) of a molecule, more particularly, with reference to the following features: centres of asymmetry, orientational and conformational stability, and proximity of pairs or sets of groups.

With regard to asymmetric centres it is apparent that the configuration of each individual centre must be taken into account, as must the influence of these centres on one another. In the extreme case in which the asymmetric centres are distant and effectively isolated from one another, the problem of stereospecific synthesis can be difficult. Possible measures for the simplification of such problems include the use of control units which allow a pre-existing centre to influence the formation of another, the use of dissymmetric reagents or catalysts, and the joining of structural units in which *all* the asymmetric centres are *preformed* with the proper absolute configuration. The last technique is illustrated by the standard synthesis of polypeptides from amino acids of a specified configuration.

Molecules in which centres of asymmetry effectively interact present different challenges and new opportunities for simplification. Often in these cases the synthetic scheme may depend greatly on the stereoisomer to be



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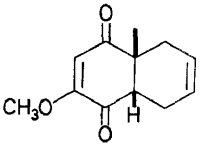

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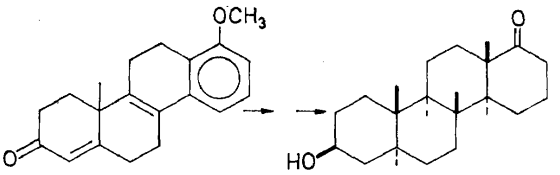
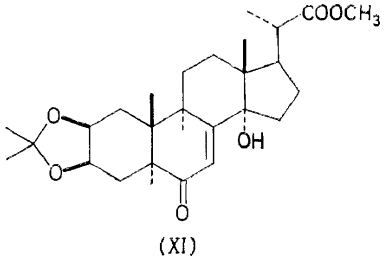


constructed. The Stork synthesis of cantharidin (IX) is a good illustration[4].

When asymmetric centres interact, the various possible stereoisomers and the transition states leading to them are of different energy. Relative stabilities then depend heavily on spatial relationships. The application of conformational analysis, the distinction between stable and unstable orientations, and the possible use of processes which equilibrate isomers all become of great importance. A stable arrangement can often be produced by processes of thermodynamic or equilibrium control as well as kinetic control. A less stable arrangement must usually (but not always) be constructed by a stereoselective, kinetically controlled process.

There are widely applicable techniques for the establishment of asymmetric centres in the less stable arrangement which depend on proximity or steric effects. Such processes, *e.g.*, the borohydride reduction of an 11-keto steroid to give the 11β-alcohol, are often described as involving attack by a reagent from the less hindered approach. By means of such reactions proximity effects can be self-amplifying and can influence more strongly the creation of further centres of asymmetry.

Several recent syntheses of decalin systems provide clear illustrations of these general statements. Many of the existing syntheses of steroids have taken advantage of the fact that the ring fusions are in the thermodynamically stable *trans* arrangement. In the Woodward total synthesis[5] the *cis* fusion, established initially in the first precursor (X) of the C/D ring system by a Diels–Alder reaction, was later modified to the desired *trans*-locked ring system by equilibration via the keto⇌enol change. The synthesis of *epi*-androsterone by W. S. Johnson[6] was greatly simplified by the *anti-trans–anti-trans* geometry, which allowed the efficient introduction of six centres of asymmetry in two steps. On the other hand, synthesis of the *cis* A/B fusion of the insect hormone ecdysone was accomplished via the intermediate (XI), which has *trans*-locked A/B rings, by an enol⇌keto equilibration, with the 2β,3β-acetonide synthon serving as controller to reverse the normal *cis–trans* energy relationship[7].



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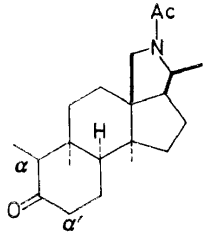

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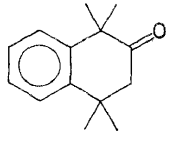

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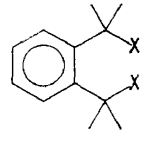
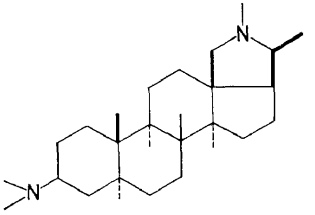


(XIV)

It may at times be desirable to design the synthesis of a thermodynamically stable structure via an intermediate with a different and relatively unstable geometry. Commonly, this indirectness is a price which is paid when the Diels–Alder reaction is applied to fused ring formation. Another interesting example occurs in Stork's synthesis of conessine[8], in which the intermediate (XII) was deliberately created (by *cis* catalytic hydrogenation) in the unstable, B/C–*cis* fusion, even though the B/C fusion of conessine is the stable *trans* form, in order to direct enolate formation in (XII) to C_{α} rather than to $C_{\alpha'}$. Of course, the correct B/C fusion was subsequently obtained by equilibration.

The spatial proximity of groups within a molecule can be of enormous consequence to synthesis. In 1,2-di-*t*-butylbenzene, for example, the proximity of the two *t*-butyl groups leads to severe destabilization and renders the classical approach for the direct introduction of a *t*-butyl group on a benzene ring unworkable. The same proximity has allowed the uncomplicated synthesis from the bicyclic structure (XIII) via (XIV; X = COOH), and (XIV; X = CH_2OTs)[9].

When an analysis of a stereostructure leads to the conclusion that strong repulsive, non-bonded interactions are present, it can be expected that any synthetic scheme which does not take full cognizance of stereochemical possibilities or problems will have a correspondingly low expectation of success. At the opposite end of the scale are cases such as adamantane, a structure of such stability that it can be reached from innumerable saturated hydrocarbons by equilibrating isomerization[10].



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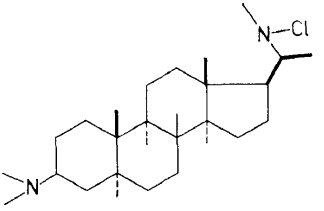


(XVI)

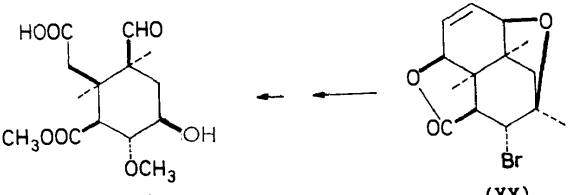
(XVII) (XVIII)

A somewhat more subtle use of proximity was involved in the synthesis of dihydroconessine (XV) from a pregnane derivative without a functional group at C_{18}. The proximity of the nitrogen substituent at C_{21} and the angular methyl C_{18} in the synthetic intermediate (XVI) directs selective free-radical attack on hydrogen at C_{18} to produce first an 18-chloro-20-amino compound and then dihydroconessine[11]. This functionalization process has subsequently been extended greatly. The reaction of alcohols with lead tetraacetate[12], and the photolysis of hypohalites[13] and nitrites[14] are now

extremely important techniques of synthesis which depend on proximity effects.

A variety of examples could be given to illustrate the use of positioned functionality for the delivery of groups to specific *reactive* centres; the charming application of the Claisen rearrangement by Burgstahler (XVII→XVIII) belongs in this category[15].

Proximity of *reactive* functional groups is of major importance in synthesis. The interactions which result from such proximity give rise to the phenomenon of "neighbouring groups", in which a reaction is channelled along a course involving temporary rings in cyclic intermediates with a major effect on rate, stereochemistry, and product distribution. Spatial proximity of functional groups obviously influences the possibilities for the use of control and equivalent synthons. Indeed, this is now almost a synthetic cliché. The Woodward synthesis of the monocyclic reserpine intermediate (XIX) via the tetracyclic structure (XX) is an instructive example[16].



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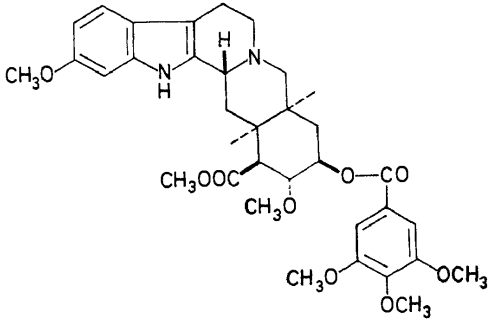
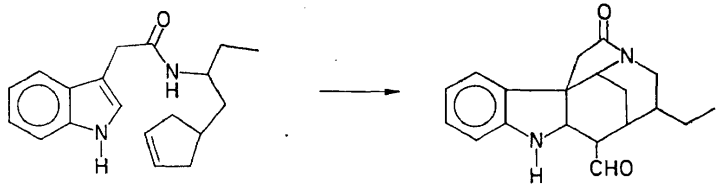


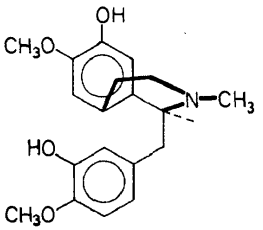
Reserpine

The two-step synthesis (XXI → XXII) of a strychnine-type structure by van Tamelen[17] represents an elegant application of rings for the minimization of functionality in a synthetic intermediate.



(XXI) (XXII)

At a slightly different level these arguments lead to the proposition that in certain synthetic problems it may be extremely helpful to induce proximity by the use of temporary bridging elements as control synthons. Such considerations suggest, for example, that the phenol coupling process (XXIII → XXIV) which provides a synthetic route to morphine and which has been found by Barton[18] to proceed in only 0·012 per cent yield, could better be carried out with an intermediate such as (XXV) in which the molecule is held in a geometry suitable for directed cyclization. It is obvious that such a synthetic technique is an intramolecular version of the intermolecular control situation which is central to the functioning of enzymatic catalysts in the synthesis of complex molecules.



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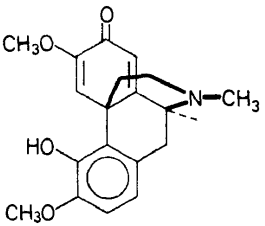

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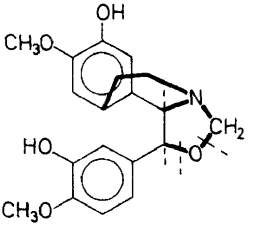


(XXV)

The use of metal ions or atoms as directing elements in synthesis is particularly intriguing. The original synthesis of phthalocyanines[19], the syntheses of macrocycles by Busch[20], the synthesis of cyclododecatriene by Wilke[21], and the brilliant work of Eschenmoser[22] on the synthesis of corrins are illustrative of the possibilities in this area.

Knowledge or enlightened speculation as to the way in which a molecule to be synthesized has previously been brought into existence can be extremely helpful in simplifying a synthetic problem. In the case of natural products, the mode of biosynthesis is relevant; in the synthesis of usnic acid (IV), referred to above, a knowledge of biosynthesis played a role in suggesting the simplified solution. In the field of alkaloid synthesis the use of biogenetic considerations has been very fruitful from the time of Robinson's pioneering synthesis of tropinone[23] to the recent scheme of Battersby for colchicine[24]. A simplification in the synthesis of α-caryophyllene alcohol came from a speculation as to the mechanism of its origin from humulene[25].

The stage of molecular simplification is not really separable from those which are described below. *Some of the most important simplifications in a synthetic problem can be uncovered only during the process of deriving a sequence of synthetic intermediates.* An operational loop must be established which allows interaction of the initial ideas for simplification with those which develop at the later stages of analysis of the problem.

When simplification has been carried to the limit, the next phase of analysis is reached—generation of further sets of intermediates. Simplification may in some instances have proceeded far enough to establish the form of a simple overall plan. Clearly, additional simplification must be sought for each successive intermediate in progressing toward the starting point for synthesis.

Generation of sequences and specific intermediates

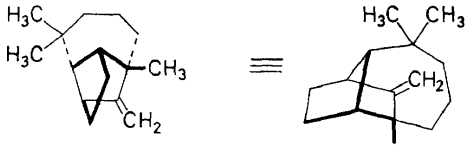
The task of devising a definite set of synthetic intermediates connected by specific synthetic operations is usually simplest for acyclic structures. Within this category, as is generally the case, a number of factors can complicate the problem, including substitution and functionality, elements of instability, and the presence of asymmetric centres. The joining of cyclic units to such an acyclic molecule usually does not provide a major complication in cases where the construction of the cyclic units themselves is trivial, *e.g.*, benzene or other standard ring systems. However, structures containing ring(s) with features not readily introduced by standard synthetic operations (the result, *e.g.*, of ring size, strain, or functionality) often present a great challenge. Furthermore, polycyclic structures which have a high degree of internal connectivity (many common atoms) present still more formidable obstacles, usually (but not always) in proportion to internal connectivity as well as substitution, functionality and sources of asymmetry. It is advantageous to consider first the general principles behind the generation of a sequence of synthetic intermediates for acyclic cases and then to examine the modifications or elaborations which may be appropriate to cyclic structures.

For acyclic molecules the recognition of important synthons is a prerequisite to the generation of possible synthetic intermediates. In the case of highly repetitive structures, *e.g.*, peptides, this exercise is so simple as to be obvious. In more highly variegated structures the recognition of synthons is both difficult and more important. Here smaller molecular fragments are generated by disconnection of synthons, either directly, after the introduction of equivalent synthons, the introduction of control synthons, or the introduction of rearranged synthons. The synthesis of methyl *t*-butyl ketone (pinacolone) provides a simple example of the value of considering rearrangement; the synthesis of 1,3-butanediol shows the value of considering equivalent synthons, since this leads to the intermediates β-hydroxy *n*-butyraldehyde and acetaldehyde. The use of cyclic intermediates to produce difunctionality is another form of the generation of equivalent synthons, *e.g.*, the change of a cyclohexene to a Δ^1-cyclopentenecarboxaldehyde via the 1,6-hexanedial system. Protecting groups and temporary rings are useful control synthons. The latter often serve to facilitate the introduction of functional groups, molecular fragments, or centres of asymmetry. From these considerations, and others which need no elaboration, it can be seen that the generation of a set of synthetic intermediates for an acyclic target molecule and the design of a synthesis include the following:

1. Simplification of problem.
2. Systematic recognition of synthons.
3. Generation of equivalent and modified synthons.
4. Addition of control synthons.
5. Systematic disconnection of synthons.
6. Formulation of the possible synthetic transformations which reform the starting structure from the derived intermediate(s).
7. Repetition of items 1–6 for each intermediate and each sequence (parallel sequences may be generated), including previously generated intermediates.

8. Generation of intermediates until the required starting point is reached.
9. Removal of inconsistencies.
10. Identification of unresolved problems.
11. Repetition of items 1–10 to generate alternative schemes.
12. Assignment of merit.

The same steps are involved in the formulation of a synthetic scheme for cyclic molecules, but some important considerations must be added. The disconnection of synthons in cyclic structures may involve the breaking of one, two or perhaps three bonds; the effect may be to break rings without the formation of fragments, to break rings with the formation of fragments or to form fragments without breaking rings. In general, more steps of disconnection will be required to arrive at simpler structures from polycyclic molecules of high internal connectivity. Further, the number of possible synthons is large in relation to molecular size, and the number of possible synthetic designs which can be devised is correspondingly great. The difficulties can obviously be compounded by the presence of exotic rings, substitution patterns or functionality. The number of synthetic schemes which can be derived for the steroid system or even for cyclic C_{15} terpenoids is impressive. Formal procedures for the systematic disconnection of the molecular network and the ordering of a synthetic analysis become a requirement. An example of such a procedure is to be found in the published work on the synthesis of longifolene (XXVI)[26].



(XXVI)

The list of items 1–12 which comprise the abbreviated directions for devising a synthesis really describes a cyclic iterative process. It should be emphasized that these directions imply that whenever a new intermediate is generated, the previously derived intermediates must be subjected to possible modifications in response to requirements which develop at a later stage in the analysis. Gradually a more self-consistent and more valid sequence should result. It also should be noted that reasonable alternative syntheses often can be formulated simply by rearranging the sequence of individual steps.

This list of items 1–12 in the set of general instructions given above bears a vague resemblance to a computer programme; its resemblance to processes by which many of the well-known syntheses of today have been conceived is presumably much better, although many more steps of analysis are implied by 1–12 than have customarily been used. Furthermore, in many successful syntheses, one can be assured, not all of the intermediates were specified in detail beforehand, if only because the chemical situations involved in the syntheses were at some stage too complex to allow clear

predictions to be made. In such cases the general outline of a synthesis serves to lend a sense of direction, and the assumption is made that the experimental results will illuminate the fine detail sufficiently to guide the synthesis through the region of uncertainty, a situation not unlike the process of climbing a mountain or traversing a wilderness without benefit of map or trail. Some of the greatest syntheses certainly were accomplished by skilled practitioners working in this venturesome vein. It is probably safe to assume that in all syntheses there is some interaction of this character between the elements of planning and of experimental execution.

The synthetic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can hardly be included in a cataloguing of the basic principles of Synthesis, but they are very real and extremely important. Further, it must be emphasized that intellectual processes such as the recognition and use of synthons require considerable ability and knowledge; here, too, genius and originality find ample opportunity for expression.

The proposition can be advanced that many of the most distinguished synthetic studies have entailed a balance between two different research philosophies, one embodying the ideal of a deductive analysis based on known methodology and current theory, and the other emphasizing innovation and even speculation. The appeal of a problem in synthesis and its attractiveness can be expected to reach a level out of all proportion to practical considerations whenever it presents a clear challenge to the creativity, originality and imagination of the expert in synthesis.

PART II

METHODOLOGY OF INDIVIDUAL STEPS

The topic which is bounded by the title of this section is essentially Organic Chemistry in *all its forms,* including known reactions, *reaction theory, stereochemistry* and *experimental practice* as well as the physical and analytical aspects of organic chemistry. It is most important for purposes of this essay to focus on synthetic operations and reactions. In general, the following basic types of synthetic transformations can be recognized:

1. Modification of chains: lengthening, shortening, branching, rearranging.
2. Formation of rings.
3. Modification of rings: cleavage contraction, expansion, rearrangement.
4. Introduction of functional groups.
5. Modification of functional groups: removal, interconversion.
6. Control operations: introduction, utilization, removal of protecting and directing groups.
7. Modification of stereochemistry.

Organic reactions and processes can be classified according to their place within the above list of operations just as validly as they can be catalogued according to mechanism. In fact, *both* classifications are necessary to

Synthesis. It is clear, in addition, that a knowledge of the selectivity, scope and stereochemistry of reactions also plays a vital part in Synthesis.

Both the analysis of a synthetic problem to produce a plan of Synthesis and the actual execution of the Synthesis depend critically on the methods available for transforming one organic substance into another. As new methods are developed, both tasks are simplified. Furthermore, the addition of new methods of Synthesis which are general and which, therefore, can be used broadly effectively multiplies the utility of previously existing methods. The importance of developing new general methods which are applicable to the synthesis of complex molecules is made even more apparent by examination of the syntheses which have been completed during the span 1945–1966, the period which encompasses most of the major achievements of Synthesis.

Almost all of the salient syntheses of this time have depended heavily on one or more synthetic methods developed subsequent to 1940. The majority of these new synthetic methods were uncovered by the systematic study of the fundamental chemistry of certain classes of organic compounds. However, new methods are now being developed at an ever increasing rate by a different approach; one in which certain synthetic operations, not allowed by pre-existing reactions, become the primary goal of research. One specific example is the search for methods for the introduction of functional groups at unactivated sites in molecules. The discovery of new methods for performing specific structural operations requires first a *realization* of certain unfilled needs in the field of Synthesis. The combination of reaction theory with a broad appreciation of classical and contemporary chemistry and a willingness to speculate and experiment is also vital.

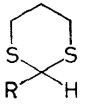
SOME NEW SYNTHETIC METHODS

In the final section of this paper, a few of the new synthetic methods which we have recently developed will be described briefly.

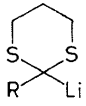
1. Symmetrization of reactivity; nucleophilic carbon from carbonyl groups

A general class of synthetic operations whose development holds great future promise is composed of processes which in some way *reverse temporarily* the characteristic type of reactivity, nucleophilic or electrophilic, of an atom in a functional group. We have described one such process which allows transformation of the normally electrophilic carbonyl carbon of aldehydes into a nucleophilic centre[27]. The carbonyl group is converted into a 1,3-dithiane system (XXVII), which can be metalated easily by *n*-butyllithium at C_2. The resulting lithio derivatives (XXVIII) undergo the whole gamut of reactions characteristic of organolithium compounds; they react with carbonyl groups and other electrophilic double bonds, with primary and secondary halides, epoxides, *etc.* Conversion of the 1,3-dithianes after such transformations to the corresponding carbonyl compound can be carried out under catalysis by acids or mercuric ion, or oxidatively with N-bromosuccinimide under mild conditions[28]. The use of these reagents has been applied to the synthesis of aldehydes, ketones, carboxylic acids, α-diketones,

α-hydroxyketones, α-aminoketones, 1,*n*-diketones, α-keto acids, β-hydroxyketones, α,β-unsaturated ketones, and even silyl ketones such as (XXIX).



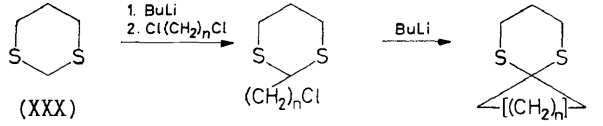
(XXVII)



(XXVIII)

(XXIX)

New methods for the efficient formation of rings from 1,3-dithianes have also been developed, as illustrated, for example, by the synthesis of a series of thioketals of cyclic ketones (XXXI) from 1,3-dithiane (XXX) and 1,*n*-dihalides.



(XXX)

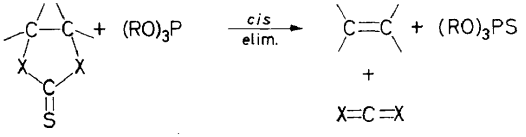
n=2-5 (55-75%)

(XXXI)

The anions derived from 1,3-dithianes represent powerful synthetic tools which in the future are likely to find frequent use in the synthesis of complex molecules. These reagents have already been applied successfully in a number of syntheses of natural products now being carried out in our laboratories, and our experiences thus far lead us to urge that these new synthetic reagents not be overlooked by those engaged in such work. The utility of the 1,3-dithiane reagents provides additional incentive for further investigations towards the discovery of new methods for symmetrizing reactivity relationships in synthesis.

2. Synthesis of olefins by stereospecific elimination

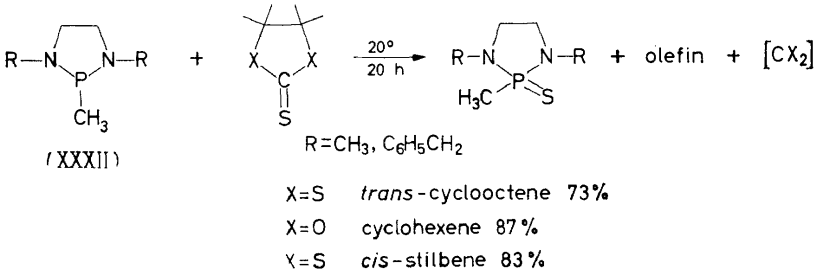
A new stereospecific and position-specific synthesis of olefins has recently been described[29] which follows the general scheme:



X=S or O

This process proceeds with complete stereospecificity by a *cis*-elimination pathway. It allows the stereospecific synthesis of strained cycloolefins, *e.g.*, *cis* or *trans* cyclooctene, the interconversion of *cis* and *trans* olefins, and even the generation of extremely unstable structures, *e.g.*, *trans*-cycloheptene[30].

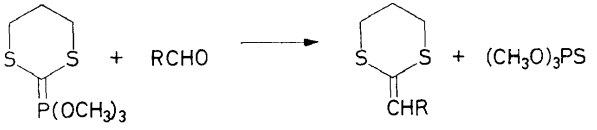
Until recently trialkyl phosphites were the most effective reagents known for this synthesis, and they were used at 100–130°. However, the diazaphospholidine (XXXII) has now been found to be more reactive by several



orders of magnitude and to permit the generation of olefins at room temperature[31].

The mildness of these conditions should allow the extension of the new olefin synthesis to a wide range of complex and/or unstable structures.

The new elimination method cannot be extended to 1,3- or γ-elimination reactions to form cyclopropanes. In the case of trimethylene-1,3-trithiocarbonate, reaction with trimethyl phosphite produces the phosphite ylide (XXXIII), which shows no tendency to decompose to cyclopropane. This ylide reacts smoothly, however, with aldehydes (but not with ketones) by a Wittig pathway[32]:



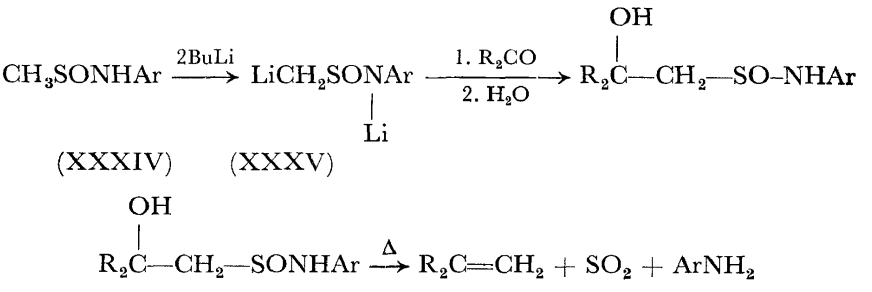
(XXXIII)

In effect this reaction provides a method for the conversion of RCHO to RCH_2COOH which is extremely selective.

3. Synthesis of olefins by coupling and stereospecific elimination

New olefin syntheses have also been developed from α-lithio sulfinamides and α-lithio phosphonamides. These involve the same overall conversion of a carbonyl to an olefinic function which is effected in the Wittig reaction, but there are important and useful differences.

Reaction of methanesulfinic acid *p*-toluidide (XXXIV) with two equivalents of *n*-butyllithium (−78°, THF) produces the dilithio derivative (XXXV)[33]. This reagent combines with ketones to form easily purified crystalline β-hydroxysulfinamides which undergo decomposition upon



heating at reflux in benzene to form olefins, sulfur dioxide, and *p*-toluidine. It is noteworthy that β-alkoxysulfinamide anions do not tend to decompose to olefins. Carbonyl adducts can also be obtained from aldehydes, but their conversion to olefins is rather less efficient than that observed with adducts from ketones; in general, the ease and efficiency of olefin formation increases with the degree of substitution at the olefinic bond.

Reaction of alkylphosphonic acid bis-dimethylamides with *n*-butyllithium (−78°, THF) leads generally to the α-lithio derivatives which react with aldehydes and ketones to form easily purified, crystalline β-hydroxyphosphonic acid amides in high yields. β-Hydroxyphosphonic acid amides undergo elimination smoothly upon heating at reflux in benzene to form olefins. These general reactions are illustrated for the specific case of methylphosphonic acid bis-dimethylamide (XXXVI).

Phosphonamide Route to Olefins

$$CH_3Cl + PCl_3 \xrightarrow{AlCl_3} \xrightarrow{H_2O} CH_3POCl_2 \xrightarrow{(CH_3)_2NH} CH_3PO[N(CH_3)_2]_2$$

(XXXVI)

$$CH_3PO[N(CH_3)_2]_2 + n\text{-BuLi} \xrightarrow{-80^\circ} LiCH_2PO[N(CH_3)_2]_2 \xrightarrow{R_2CO}$$

$$R_2\overset{OH}{\overset{|}{C}}CH_2PO[N(CH_3)_2]_2 \xleftarrow{H_2O} R_2\overset{O^-}{\overset{|}{C}}CH_2PO[N(CH_3)_2]_2$$

$$\downarrow \Delta$$

$$R_2C{=}CH_2 + [(CH_3)_2N]_2POOH$$

$$i\text{-PrCl} \rightarrow i\text{-PrPO}[N(CH_3)_2]_2 \xrightarrow[\text{etc.}]{\text{1. BuLi}\ \text{2. } (C_6H_5)_2CO} (C_6H_5)_2C{=}C(CH_3)_2$$

Certain potential advantages of the phosphonamide route to olefins as compared with the Wittig reaction can be cited. (1) The reagents are readily available and potentially much cheaper, especially on a molar basis. (2) The elimination of β-hydroxyphosphonic acid amides to form *cis* or *trans* olefins is stereospecific. Therefore, by controlling or modifying the configuration of the intermediate, either a *cis* or *trans* olefin can be generated. Thus, this olefin synthesis also allows control over both geometry and position of the ethylenic unit. The synthesis of *cis*- and *trans*-1-phenylpropene can be carried out stereospecifically by elimination from the diastereomeric adducts (XXXVII). (3) The α-lithio phosphonic acid amides can be alkylated efficiently, in contrast to phosphonium ylids as is shown by the formation of (XXXVIII).

Experimental data on the advantages of phosphonamide route to olefins are provided in *Tables 1* and *2*.

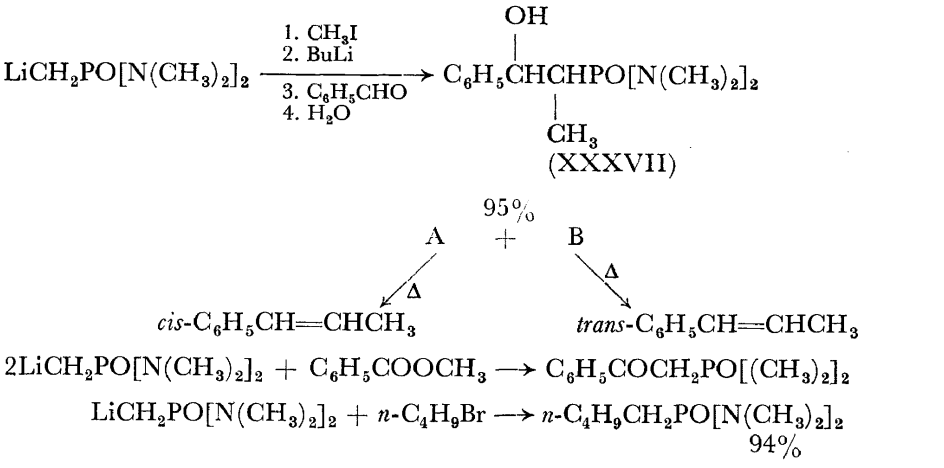


Table 1. Conversion $R_1R_2C{=}O \rightarrow R_1R_2C{=}CH_2$ via methylphosphonic acid (Bis-dimethylamide adducts)

Carbonyl Compound	*Yield of adduct* (%)	*Yield of olefin* (%)
Benzophenone	95	93
4-*t*-Butylcylohexanone	98	65
2-Cyclohexenone	96	78
Benzaldehyde	95	53
Δ^3-Cyclohexenecarboxaldehyde	95	67
Dodecanal	89	70

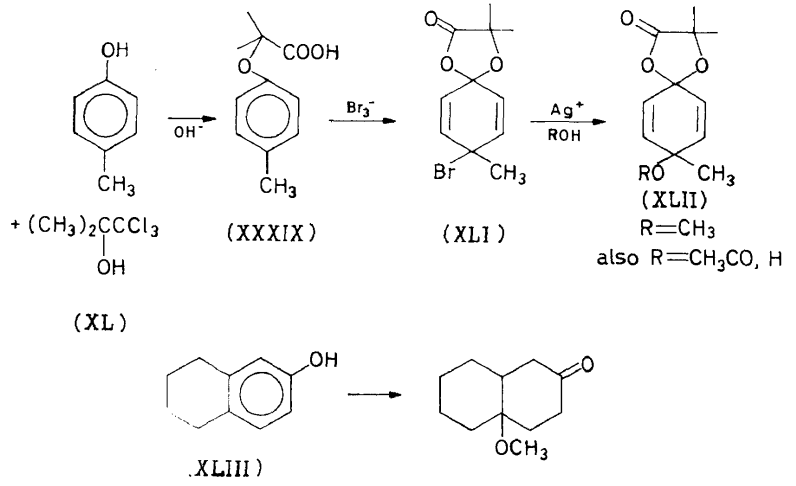
Table 2. Conversion $R_1R_2CO \rightarrow R_1R_2C{=}CHCH_3$ via ethylphosphonic acid (Bis-dimethylamide adducts)

Carbonyl Compound	*Yield of adduct* (%)	*Yield of olefin* (%)
Benzophenone	97	90
4-*t*-Butylcyclohexanone	92	80
Benzaldehyde	98	54
Δ^3-Cyclohexenecarboxaldehyde	96	79

4. Selective reduction of phenolic rings

The last of the new methods to be discussed is a process which allows the reduction of phenolic rings under extremely mild conditions and which was expressly designed for application to the synthesis of carbocyclic natural products and other complex molecules. There is a need for such a procedure, since the presently known methods, high-pressure catalytic hydrogenation and alkali metal–ammonia (Birch) reduction, are subject to severe limitations in complex molecules with reducible or base-sensitive functional groups. The method is illustrated with *p*-cresol. In the first step the phenol is etherified to form the isobutyric acid (XXXIX) by reaction with chloretone

(XL) and base. Reaction of (XXXIX) as the sodium salt with bromine at −20° in aqueous dimethyl sulfoxide produces a bromolactone (XLI) which can be isolated and converted by reaction with silver ion in methanol to a methoxy lactone (XLII). The methoxy diene lactone (XLII) is very easily reduced and is easily converted to a variety of derivatives of 4-methylcyclohexanone by standard mild procedures. This method has also been applied to polycyclic structures such as (XLIII).



Many of the ideas presented here are generalizations of concepts and principles which have been developed and demonstrated by those who have been engaged in the synthesis of specific complex molecules over the past few decades. It is the hope of the author that this attempt to present the methods of organic synthesis in a general form will serve to emphasize the importance of their achievements as well as to clarify some of the underlying methodology.

The discussion in Part I has doubtless been influenced to some degree by the writer's personal experience. Other modes of thought, other interests might well have produced a different view, especially of the subsidiary details. It is hoped that a much more systematic, rigorous and complete account of the logic of Synthesis and the basic data with which it operates can be given in the near future.

Mention should be made to two superb general accounts of Synthesis, written by one of the Grand Masters[34,35]*, which are highly recommended to those interested in a broad view of the subject.*

Finally, the writer acknowledges his indebtedness to a splendid group of collaborators for the accomplishment of the work outlined in Part II. These gentlemen by name are: Dieter Seebach, Roland A. E. Winter, Francis A. Carey, Charles Cumbo, Gottfried Märkl, Tony Durst, George Kwiatkowski, Sandor Barcza and Georg Klotmann. The U.S. National Science Foundation and National Institutes of Health provided financial support.

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