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# PRESENT-DAY METHODS OF SYNTHESISING MACROCYCLIC COMPOUNDS

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## 1. INTRODUCTION

During the past 10–15 years the chemistry of macrocyclic compounds has been transformed from a relatively little studied section of organic chemistry into one of its most vigorously developing branches. The progress achieved by the present time is shown in the creation of new methods of synthesising macrocycles, the study of the specific physical and chemical properties of the simplest members of this class of compounds, and the investigation of complex natural products containing large and medium rings† as structural units.

The study of macrocyclic compounds is of considerable interest in the theory of organic chemistry. Compounds of this type exhibit very clearly the effect of various steric factors on physical properties and chemical behaviour. In virtue of the peculiar "compactness" of many-membered rings, especially those of medium size, substituents which are not directly linked together prove to be contiguous in space, and opportunities are created for the interaction of atoms and groups located on opposite sides of the ring (transannular effect). The investigation of macrocylic compounds has substantially extended and deepened our ideas on strain in rings and has revealed interesting information on the relation between the strain in and the reactivity of a ring. Finally, the study of the molecular structure of macrocyclic compounds, by such methods as X-ray structural analysis, infrared spectroscopy, and measurement of dipole moments, has given extremely valuable information on the relative arrangement of atoms in a many-membered cyclic molecule. These results together with calculations of the energetically most favourable conformations by the use of electronic computers will undoubtedly lead to the further development of conformational analysis in the immediate future. More detailed accounts of the above questions will be found in review papers[2-4].

Quite recently, in connection with the synthesis of the cyclic system termed a catenane, in which two rings are combined as links in a chain[5,6], most interesting questions have been posed concerning new forms of isomerism in macrocyclic compounds, solution of which will require

† At the present time macrocyclic compounds comprise those containing medium rings (8–12 atoms) and large rings (13 and more atoms). Small rings (containing 3 and 4 members) and normal rings (5-, 6-, and 7-membered) are combined into groups of so-called "classical" rings[1].

application of the elements of topology. These investigations will undoubtedly give an impetus to the further development of our seemingly established views of the molecule, since in a catenane the two rings are combined, not by a chemical bond, but "mechanically" as it were, and it still remains an open question whether the catenane system should be regarded as one or two molecules.

On the other hand, investigation of natural products has revealed the important biological role of macrocyclic compounds. Not long ago, physiologically active macrocyclic compounds comprised only a few alkaloids, porphyrins, and some perfumes; at the present time a large and ever increasing number of natural macrocyclic compounds are known with a clearly marked physiological activity (see for example Refs 7–14). Many alkaloids, for example tubocurarin, such hormones as oxytocin and insulin, and antibiotics, *e.g.* macrolides, gramicidin S, enniatin, valinomycin, etc., are macrocyclic compounds. It may be supposed that in many cases a macrocyclic structure is a necessary precondition for the presence of a biological effect. In this connection, work on the synthesis of macrocyclic compounds of potential biological activity has begun to be intensively developed. Among macrocyclic compounds which have been synthesised are substances having a curarelike[15], anticholinergic[16], and hypotensive action[17], analgesics[18], anaesthetics[19], and also weed-killers[20], insecticides[21,22], and growth promoters[22].

From what has been said it is clear that the development of new methods for synthesising macrocyclic compounds is an extremely urgent task. Many papers have been published on the preparation of macrocyclic compounds, their number growing continually and probably amounting at the present time to many hundreds. Without aiming at an exhaustive survey, we intend to systematise the most important achievements in the synthesis of macrocyclic systems‡, and refer the reader to Ziegler's fundamental review[23] published in 1955, which covers the literature up to September 1953. Here we shall be concerned mainly with more recent literature, referring to the earlier work only when necessary to make the exposition complete. The history of the chemistry of macrocyclic compounds will not be discussed, since a very detailed literature already exists on this topic (see in particular Refs. 24 and 25).

In my view the extensive literature on the synthesis of macrocyclic compounds can usefully be classified according to the type of reaction resulting in formation of a many-membered ring rather than according to the class of compound formed. The various reactions leading to the formation of macrocycles can be grouped in four fundamentally different types — (1) cyclisation, (2) depolymerisation, (3) syntheses involving a transannular bond, and (4) ring enlargement and contraction.

## 2. METHODS OF CYCLISATION

Macrocyclic systems have hitherto been obtained most frequently by the cyclisation of long-chain bifunctional compounds. The synthetic chemist now has at his disposal various methods of cyclisation enabling him to obtain acceptable yields of the most diverse macrocyclic systems. the chief obstacles to be overcome occurring quite frequently in the synthesis of the initial long-chain compounds and not in the process of cyclisation. However, ring-closure of the macrocycle itself is associated with several specific difficulties, which emerge more or less strongly with all methods of cyclisation. Before passing to an account of individual methods of cyclisation, therefore, let us examine some of the thermodynamic and kinetic factors which control the process, as well as the structural features of bifunctional compounds which facilitate cyclisation.

The difficulties associated with the preparation of macrocyclic compounds by processes of cyclisation are due to the low probability that the ends of a long chain will meet[26]. The tendency to ring formation is a complex function of the distance between the reactant groups and the loss of entropy associated with its fixation, the Baeyer strain, the Pitzer strain, and the contraction of the van der Waals radii[3,4].

Two reactions — intramolecular (ring formation) and intermolecular (polycondensation or polymerisation) — are in competition during cyclisation. In all cases other than the formation of five- and six-membered rings, the intermolecular reaction is thermodynamically the more advantageous[27,28]. However, the possibility of cyclisation is determined not only by thermodynamic but also by kinetic factors. Macrocyclic compounds, which were originally obtained in very low yields[29], can now be synthesised in quite high yields (see below and also the review in Ref. 23)§. This is achieved primarily by the use of high dilutions during cyclisation. The principle of high dilution, proposed by Ruggli[30], was first applied by Ziegler[31]. Under these conditions opportunities for intermolecular reaction are limited, while intramolecular cyclisation becomes more probable.

Apart from dilution, ease of cyclisation is affected by various structural factors which make more or less probable the occurrence of chain conformations which are convenient for cyclisation. For example, replacement of a methylene group in a bifunctional compound by oxygen usually results in an increased yield of the cyclic compound (the "oxygen effect" [23,32-34]), which can be explained by a diminution in conformational strain on substitution of a quadrivalent by a bivalent atom. The presence of rigid groups (multiple bonds, aromatic rings) in the chain of the compound to be cyclised decreases the mobility of the chain, and hence also the total number of possible conformations, so that favourable conformations become more probable and the yield of the macrocyclic compound is increased ("the rigid group principle" [23,25,35])¶. Ease of cyclisation can depend not only on ring size but also on whether the number of cyclic atoms is odd or even, since in several cases formation of a "coiled" chain with its ends close together, and not containing thermodynamically unfavourable

‡ The review does not cover inorganic macrocyclic compounds such as the cyclic siloxanes and phosphonitriles: it is confined to carbocyclic and "normal" heterocyclic compounds, the latter containing oxygen, sulphur, or nitrogen as hetero-atom.

§ Nevertheless, it must be remembered that compounds having medium rings, in which so-called "non-classical" strain is inherent[3], are obtained in lower yields, whatever the method of cyclisation used, than the strainfree compounds having large rings (*e.g.* Ref. 23).

¶ This statement concerning the influence of rigid groups relates, of course, to the synthesis of macrocyclic systems, but is not applicable to the formation of compounds containing normal rings.

eclipsed conformations, is possible only with chains having an odd number of members[34,36].

The probability of cyclisation can be increased by the presence in a bifunctional compound of even short substituent side-groups, restricting internal rotation. As a result, the chain can more often adopt "coiled" conformations with the functional groups close together and favouring cyclisation[34,37,38].

The influence of substituents on cyclisation is especially clearly developed in the synthesis of rings of medium size (8–12-membered)[39,40]. The presence of substituents plays an important part also in the preparation of small and normal rings. The opinion has even been expressed[41] that in general "the presence of substituents and their nature are of greater significance for the ease of formation and the stability of a ring than is the number of atoms in the ring alone".

In general it can be stated that the increase in rate of cyclisation accompanying introduction of substituents is caused primarily by the conformational effect[42]. Substituents favour an increase in the content of the gauche form at the expense of the transoid form, as a result of which the reactant groups occupy positions in which cyclisation is possible. More simply, if it is accepted[34] that the most favourable form for a polymethylene chain is a planar zigzag in which the ends of the chain (the functional groups) are as remote as possible from one another, substituents when present may become involved in the zigzag, and bring the functional groups closer together.

When the chain of a bifunctional compound contains several substituents, the compound usually contains several asymmetric atoms. In such cases the probability of the occurrence of a conformation convenient for cyclisation may be determined also by the steric configuration of its individual sections: in other words diastereoisomers may differ markedly in their capacity for cyclisation[43].

Bulky substituents near reactant groups may increase the probability of cyclisation not only by their effect on the conformation of the chain but also because they create steric hindrance to the intermolecular reaction. In fact, the use of bifunctional compounds containing large substituents makes it possible in several cases to obtain macrocycles without the employment of high dilutions[44,45].

The greater or lesser probability of the production of a favourable form of the chain will depend also on the mechanism of cyclisation. Thus in the acyloin condensation of dicarboxylic esters, which is carried out in heterogeneous medium, the probability of the alkoxycarbonyl groups coming together is increased by chemisorption on the surface of fused metallic sodium[32,46].

Let us examine some problems associated with the practical application of the high dilution principle. As noted above, the competing polymerisation or polycondensation is suppressed to a greater extent the lower the concentration of the cyclisable substance. In order to avoid increasing unduly the volume of the reaction mixture, this substance is usually introduced slowly into a moderate quantity of solvent containing a condensing agent or present under conditions (temperature, illumination, etc.) to ensure the occurrence of the reaction. In many cases the solvent is kept boiling vigorously, the condensate being used to dilute the substance undergoing cyclisation; the latter is therefore introduced into the reaction space in very dilute form, and thus the possibility of a local increase in concentration is excluded ("high dilution technique")†. Thus, instead of increasing the volume we increase the duration of the process.

In a chemical reaction which is carried on for a long time a point can be reached at which as much reactant enters the reaction zone in unit time as is removed from it by the reaction. Actually, if reactant is supplied at a constant rate $(dc/dt)_f$, while its rate of consumption is $-(dc/dt)_r = kc^n$‡, where $(dc/dt)_f > -(dc/dt)_r$, the concentration $c$ will increase continuously, at the same time accelerating the consumption of reactant, so that at some instance the accumulation of the reactant will lead to the equation $(dc/dt)_f = -(dc/dt)_r$, which corresponds to a steady-state concentration $c_{st}$ (at a given rate of supply this instant will occur sooner the greater is $k$)§. For a given feed rate this concentration is constant. If supply is slowed down, which corresponds to the condition $(dc/dt)_f < -(dc/dt)_r$, more of the substance will be consumed than is supplied, and a new stationary concentration $c'_{st} < c_{st}$ results.

In the case of the reactions under consideration here, taking place under conditions of high dilution, the stationary concentration determines the preferred direction of the process (formation of either a macrocyclic compound or a high polymer)[23]. The stationary concentration of the cyclisable substance depends not only on the rate of addition of the latter and the volume of the solvent but also, what is especially important, on the rate constant of the reaction. Different ring-closure reactions therefore require substantially different conditions of dilution, or give different results under the same conditions of dilution.

Let us examine by way of illustration two reactions obeying the same kinetic equation but differing in their rate constants (in particular, they may be represented by the same reaction in the presence of two different catalysts). In this case the stationary concentration $c_{st}$ will obey the equation

$$\left(\frac{dc}{dt}\right)_f = -\left(\frac{dc}{dt}\right)_r = kc_{st}^n$$

whence

$$c_{st}^n = \frac{1}{k}\left(\frac{dc}{dt}\right)_f.$$

† In several cases, when the solubility of the cyclisable substance in the solvent used is negligible and the reaction is carried out in a heterogeneous medium, macrocyclic compounds can be obtained in a small volume of solvent without application of the high dilution technique (*e.g.* Ref. 47).

‡ The reaction velocity may depend not only on the concentration of the cyclisable substance but also on that of the condensing agent. However, the latter can be regarded as constant, so that all the arguments remain valid.

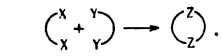
§ Strictly speaking, a stationary concentration is established if the duration of the reaction is infinite. If, for example, the substance is fed at a constant rate $w$, while it is consumed according to a first-order equation, the increase in concentration in the solution in unit time is $dc/dt = w - k_1c$. Integrating this expression, we obtain $t = -(1/k_1)\ln(1 - k_1c/w)$ or $k_1c/w = 1 - \exp(-k_1t)$. The condition of stationariness $k_1c/w = 1$ corresponds to $t = \infty$. In practice, however, the quantity $\exp(-k_1t)$ will become relatively small after a time determined solely by the rate constant. Thus if $k_1 = 0.1\ h^{-1}$ we have $k_1c/w \simeq 0.63$ after 10 h; if $k_1 = 1\ h^{-1}$ this ratio exceeds 0.99 even after 5 h; and when $k_1 = 10\ h^{-1}$ this state is reached after only 30 min.

If for two reactions ($a$ and $b$) we choose the same rate of feed $(dc/dt)_{f,a} = (dc/dt)_{f,b}$, where $k_a > k_b$, we have $c_{st,a} < c_{st,b}$: *i.e.* the more rapid reaction corresponds to a lower stationary concentration, and so conditions will be more favourable for formation of the macrocyclic compound (*cf.* Ref. 48).

These relations apply also to the same reaction at different temperatures. Increase in the reaction rate constant with rise in temperature should result in a decrease in the steady-state concentration, just as should the use of a more active condensing agent. The upper temperature limit at which a given reaction can be carried out will, of course, depend on the thermal instability of starting materials or reaction products. In the high dilution technique variation in temperature depends on the choice of a solvent which is inert under the reactions conditions and boils at the required temperature. It must be noted that interaction of the solvent with the cyclisable substance may substantially affect the process of cyclisation by favouring either the "coiled" or the "open" form of the chain[23].

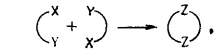
When reactions which occur at high dilutions are under discussion, it quite often becomes necessary to compare degrees of dilution. For this purpose we can use the relation[23] $m/Vt$, where $m$ is the quantity of cyclisable substance, $V$ the volume of solvent, and $t$ the time during which the cyclisable substance is supplied. This ratio represents the quantity of cyclisable substance fed to unit reaction volume in unit time¶.

One variety of cyclisation is the synthesis of macrocyclic systems from two or more parts according to the scheme



Such a reaction undoubtedly takes place in two stages, with intermediate formation of a bifunctional compound of the type X–Z–Y.

Formation of a macrocycle from two segments is more difficult than direct cyclisation, since the high dilution required for the second stage of the reaction hinders occurrence of the first stage[23]. Therefore the synthesis of macrocycles from more than one segment yields good results only in especially favourable cases, for example if rigid groups are present in the initial compounds. This applies also to dimerisation of a bifunctional compound according to the scheme



which quite often accompanies normal cyclisation.

Actual methods of cyclisation are extremely varied, and can lead to macrocyclic compounds of various types (carbocyclic and heterocyclic, containing multiple bonds or aromatic rings, with various substituents). For brevity we shall merely mention the methods covered by Ziegler's review[23], and discuss in greater detail new work, selecting that concerned with a new reaction employed for cyclisation, and disregarding the routine application of an existing method.

¶ It is readily seen that $m/Vt = (dc/dt)_f$, and hence, if it is assumed that cyclisation is a first-order reaction, while the competing intermolecular reaction (polymerisation or polycondensation) is of the second order, it follows that

$$\frac{m}{Vt} = k_1 c_{st} + k_2 c_{st}^2.$$

If $c_{st}$ is sufficiently small for the term $k_2 c_{st}^2$ to be neglected, we obtain $m/Vt \simeq k_1 c_{st}$.

## Condensation of Dinitriles

The first preparative method of cyclisation employed for the synthesis of macrocyclic compounds was the condensation of dinitriles in the presence of sodium methylaniline using Ziegler's high dilution technique[31]. This method has been used to synthesise keto-nitriles containing rings of different sizes; the data obtained on the dependence of yield on ring size[49,50] have been repeatedly discussed in the literature and compared with yields obtained by other methods (see in particular Refs. 23, 34, and 46).

## Cyclisation of Esters by the Dieckmann Reaction

The chemistry of this method is similar to that of the cyclisation of dinitriles, but this reaction has not been widely used in the formation of macrocycles because of the low yields obtained. It can serve for preparative purposes only if potassium t-butoxide or sodium hydride is employed as condensing agent and if the reaction is carried out in boiling xylene, the alcohol evolved in the reaction being distilled off. This procedure has been employed to obtain both carbocyclic and heterocyclic compounds. A more detailed account will be found in Ref. 51.

## Cyclisation of Dicarboxylic Esters by the Acyloin Type of Condensation

This method has found the widest application for the synthesis of macrocyclic compounds. The reaction is carried out in boiling xylene over finely divided metallic sodium under the conditions suggested by Hansley[52] and worked out in detail by Prelog[53], Stoll[54], and their coworkers. It has already been mentioned above that chemisorption of an ester on the surface of molten sodium favours cyclisation. An important feature of the acyloin condensation is the very high reaction velocity under the given conditions, resulting in a low steady-state concentration of the diester. Because of this the yields of cyclic acyloins are quite high even without use of the high dilution technique. It is important to note that the acyloin condensation does not show such a sharp fall in yields in the range of medium rings as is characteristic of other methods. A disadvantage of the acyloin condensation is a certain experimental complexity: reaction must be carried out in the almost complete absence of oxygen with the use of a high-speed stirrer (rate of rotation of the order of 10 000 rev/min). Some modifications of the conditions of this condensation will be examined at the end of the present paper in connection with the problem of the synthesis of bicyclic systems containing a thiophen ring. It is noteworthy that in the seventeen years since publication of the work of Prelog and Stoll the method of carrying out the acyloin condensation has undergone no substantial change. Hence there is no need to discuss this reaction further.

## Cyclisation by Intramolecular Alkylation

In several cases good results are obtained by this method. The cyclisation of $\omega$-halogenoacylacetic esters to carbocyclic $\beta$-keto-esters developed by Hunsdiecker[55]

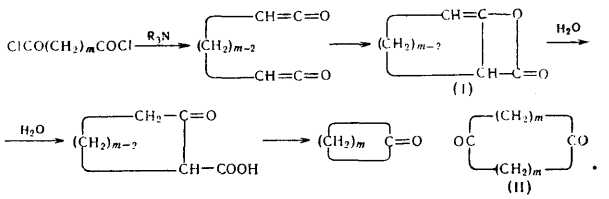
is well known. Several new applications of this reaction will be considered at the end of the paper.

Cyclisation of salts of long-chain ω-halogenoalkanoic acids to macrocyclic lactones is carried out under similar conditions. Among the papers of this latter reaction we shall mention only a fairly recent publication[56] on the kinetics of lactonisation.

Below we shall consider several new methods of cyclisation as well as some of the earlier methods which have recently found wide application.

## Dimerisation of Ketens

An interesting method of obtaining macrocyclic ketones was developed by Blomquist and his coworkers[57,58]. It is based on the dimerisation of ketens. Dichlorides of dibasic acids are converted by the action of tertiary amines into diketens, which under the conditions of high dilution undergo cyclisation to form analogues of the dimers (I). These "cyclic dimers of keten" are hydrolysed to β-keto-acids, which are readily decarboxylated, so that the reaction products are cyclic ketones. Formation of monoketones is accompanied by that of diketones of the type (II), products of the cyclisation of two molecules of the diketen.



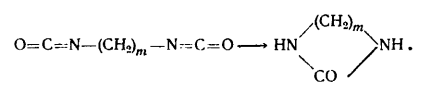
(I)

(II)

Yields of this method are low (20–30%), but its simplicity enables it to be utilised for preparative purposes. In particular, civetone and (±)-muscone[58], as well as optical isomers of the latter[59], have been obtained in this way. An advantage of the method is the possibility of using relatively short-chain dicarboxylic acids, as can be seen in the synthesis of cyclohexadecanone[60]. Azelaoyl dichloride gives a 34% yield of cyclohexadecane-1,9-dione (II, $m = 7$), which is converted into a monothioacetal, this giving a 47% yield of cyclohexadecanone (based on the diketone) under the influence of Raney nickel.

Reduction of diketones over platinum gives hydroxy-ketones, from which cyclic homologues of civetone are formed by dehydration[61].

An analogous method in the heterocyclic series is the cyclisation of diisocyanates to cyclic ureas[62–65]:



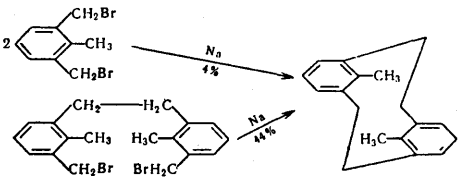
The latter method is probably similar in its chemistry to the cyclisation of azides of amino-acids under the conditions of the Curtius rearrangement, used for the preparation of unsymmetrical cyclic ureas[66].

## Intramolecular Acylation

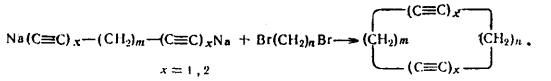
Intramolecular acylation by the Friedel–Crafts reaction has recently been widely developed, and has been investigated mainly by Huisgen and his coworkers on ω-phenylalkanoyl[48,67,68], ω-*p*-tolylalkanoyl[69], ω-1-naphthylalkanoyl[70], and ω-2-naphthylalkanoyl[71] chlorides as examples. We shall consider this method in greater detail at the end of the present paper, and note merely that cyclisation leads to products of different structures depending on the length of the aliphatic chain. For example, with ω-phenylalkanoyl chlorides $C_6H_5(CH_2)_mCOCl$ up to $m = 7$ cyclisation takes place in the *ortho*-position, but when $m \geq 8$ it occurs in the *para*-position.

## Wurtz Reaction

Another classical process, the Wurtz reaction, also finds limited application in the synthesis of macrocyclic compounds. An interesting variant of the method is replacement of metallic sodium by its addition products with arylethylenes and aryl-dienes, in particular disodium tetraphenylethylene[72]. When the Wirtz reaction is used, the macrocycle is quite often built up from two segments. In this connection, a recent paper shows that such intermolecular cyclisation gives poorer results than intramolecular cyclisation[73]. In the synthesis of 4,12-dimethyl-[2,2]metacyclophane, yields at the cyclisation stage amount to 4% and 44% by the first and second methods respectively:



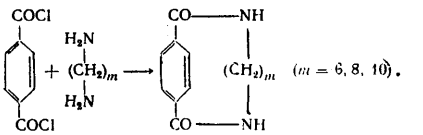
A similar mechanism to the Wurtz reaction is shown by the preparation of cyclic di- and poly-acetylenes from αω-dibromoalkanes and disodium derivatives of αω-diynes (see for example, Ref. 36):



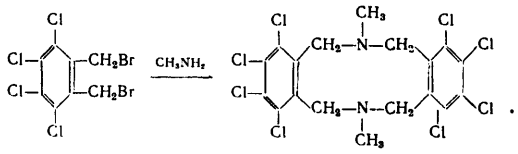
The paper referred to reports an interesting case of a "negative oxygen effect", the yield of the macrocyclic compound decreasing on introduction of oxygen into the chain. This phenomenon is explained[36] by an increase in the mobility of the cyclisable chain, resulting in an increase in the total number of possible conformations and thereby diminishing the effect of the rigid acetylenic groups.

## Syntheses of Many-Membered Heterocycles Containing Aromatic Rings from Two or More Units

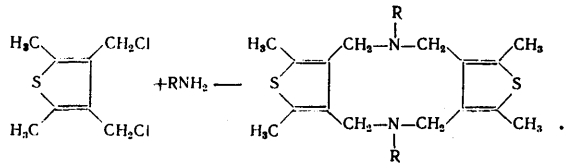
Several examples have been reported in which macrocycles are built in good yields from two or more units. We may note here the syntheses by Stetter and his coworkers of many-membered systems containing nitrogen and sulphur[74,75], for example



An interesting synthesis is that of the ten-membered dibenzodiazecine system, in more than 50% yield without use of the high dilution technique[76]



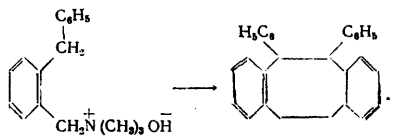
It is significant that under the same conditions the unsubstituted *o*-bisbromomethylbenzene gives high yields of *N*-methylisoindoline. Gol'dfarb and Kondakova have shown[77] that a ten-membered ring is readily formed also by reaction of 3,4-bischloromethyl-2,5-dimethylthiophen with primary amines:



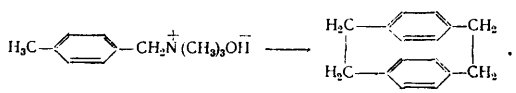
Such ease of formation of a ten-membered ring is unexpected. Gol'dfarb and Kondakova show[77] that this phenomenon is associated with the difficulty of cyclising a five-membered ring on to a thiophen ring, which is explained by the larger external angles associated with thiophen than with benzene (the $HC_{(3)}C_{(4)}$ angle is about 124° compared with 120°). It is possible that a somewhat similar phenomenon occurs in the case of tetrachloro-*o*-bisbromomethylbenzene. Polyhalogenobenzene molecules are known to be non-coplanar because of mutual repulsion between the halogen atoms, neighbouring halogen atoms being located on different sides of the ring (see, for example, data for hexachlorobenzene[78]). It is reasonable to assume that such non-coplanarity would hinder formation of a five-membered ring in comparison with the unsubstituted *o*-bisbromomethylbenzene. It may be added that in both cases cyclisation is favoured by the presence of rigid groups, and furthermore the diazecine system condensed with two benzene or thiophen rings may be considerably less strained than, for example, cyclodecane. However, the latter hypothesis requires experimental confirmation.

## Syntheses *via* Quaternary Ammonium Bases

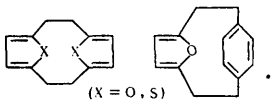
A very interesting method of preparing macrocyclic compounds containing aromatic rings which has recently been developed resembles chemically the Hofmann cleavage of quaternary ammonium bases. In the case of *o*-aralkylbenzylammonium hydroxide the Hofmann reaction yields substituted dibenzocyclooctadienes[79-82] for example



*p*-Aralkyl- or *p*-alkyl-benzylammonium hydroxides give the corresponding [2,2]paracyclophanes[83-85], for example



Similar methods have produced furan[84,85] and thiophen[84] analogues of [2,2]paracyclophane of the types

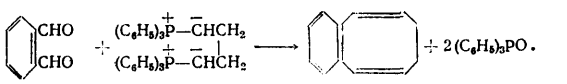


The mechanism of this cyclisation is not altogether clear. It is probable that intermediate compounds of *o*- or *p*-xylylene type are formed[84-87]. It is quite possible, however, that the reaction mechanism involves formation of an intermediate cyclic complex, as is indicated by the fact that substituents in the resulting macrocycle are always attached to adjacent carbon atoms, while structural isomers are not detected (see for example Refs. 81 and 83).

The comparatively high yields of the products obtained by this method (on the average about 30%), without requiring high dilution, are probably explained by the effect of the rigid groups.

## Cyclisation by Means of the Wittig Reaction

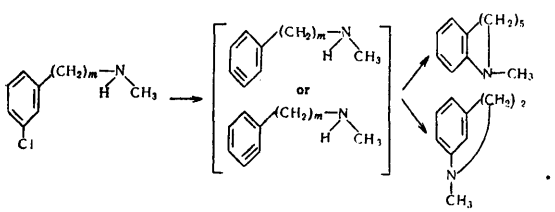
The Wittig reaction has also been used for the synthesis of macrocyclic compounds, although this method has not yet found wide application for this purpose. In 1958 Wittig and his coworkers described[88] the preparation of benzocyclooctatriene by the interaction of phthalaldehyde and the ylide formed from 1,4-dibromobutane and triphenylphosphine:



A synthesis of tetrabenzocyclohexadecaoctaene has been reported[89] in which the Wittig reaction has been used both to extend the chain and to close the macrocycle. Yields by this method are around 20–35%.

## Cyclisation *via* Arynes

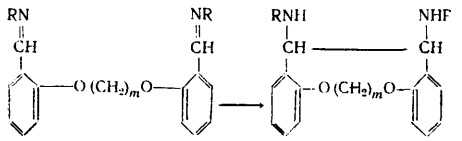
Among new methods must also be mentioned the synthesis of many-membered heterocycles containing a benzene ring by Huisgen and his collaborators[90,91]. This method uses the dehydrobenzene reaction and consists in the interaction under conditions of high dilution of a *m*-chloro-*N*-methylaminoalkylbenzene with sodamide or phenyllithium. Two examples of the reaction have so far been examined, and these show that cyclisation occurs in the *ortho*-, *meta*-, or *para*-position depending on the length of the aliphatic chain.



In the second case the *para*-cyclisation product is obtained as impurity (about 10% of the total quantity). Yields by this method are around 60%.

### Cyclisation of Bisazomethines

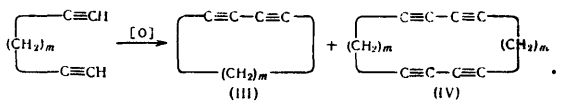
Another new method of synthesising macrocycles is the cyclisation of dianils by the action of finely divided metallic sodium[92] in ether or of aluminium amalgam[93] in a mixture of benzene and alcohol under conditions of high dilution. The reaction is essentially



Yields by the first method do not exceed 16%, and by the second fluctuate depending on $m$ and R, reaching 40–60% with $m$ = 3–9 and R = t-$C_4H_9$.

### Oxidative Condensation of Diacetylenes

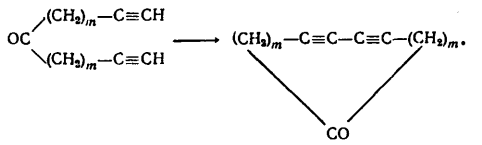
During the past six to eight years great progress has been made by the application of a new method of cyclisation based on the oxidative condensation of monosubstituted acetylenes. The long known method of condensing acetylenes in the presence of copper salts when applied to alka-$\alpha\omega$-diynes provides a route for the preparation of macrocyclic diacetylenes. In 1956 Eglinton and Galbraith[94] obtained from tetradeca-1,13-diyne under conditions of high dilution cyclotetradeca-1,3-diyne (III, $m$ = 10) in yields up to 40%, with simultaneous formation of about 10% of the dimer (IV, $m$ = 10):



Oxidation was effected with copper(II) acetate in a mixture of methanol and pyridine. Carrying out the reaction at smaller dilutions decreases the yield of the "monomer", while that of the "dimer" increases.

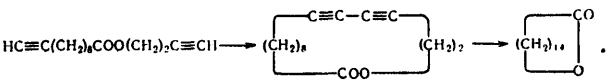
Almost simultaneously Sondheimer and his coworkers[95,96] obtained intermolecular cyclisations products of the type (IV) from the lower alkadiynes CH⋮C.$(CH_2)_m$.C⋮CH with $m$ = 3–5. Oxidation was effected with air in aqueous alcohol at 55° in the presence of copper(I) chloride and ammonium chloride without use of the high dilution technique. Yields were low (2–12%) under these conditions, but subsequently, by using copper acetate in pyridine, Sondheimer *et al.*[97] obtained, together with "dimers", the "trimers", "tetramers", and in some cases "pentamers" in total yields of up to 40%. These products are easily separated by chromatography. From a purely preparative point of view, of course, this work of Sondheimer and his collaborators may be of no special interest, but it opens up a path to the preparation of many-membered conjugated cyclic polyenes, several of which, in conformity with Hückel's rule, should be aromatic in character[98–105].

The oxidative condensation of diacetylenes can be used not only to obtain hydrocarbons but also to synthesise functional derivatives, as well as heterocyclic compounds. Recently Bergel'son *et al.*[106] have described the preparation of cyclic diacetylenic ketones by the general reaction



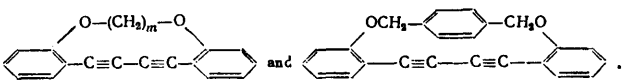
When the high dilution technique is used the yield is about 60% with values of 6 and 8 for $m$. The resulting ketones on hydrogenation give cycloalkanones, and in particular dihydrocivetone is obtained when $m$ = 6.

This method has been used repeatedly to obtain cyclic esters[94,107–112], including those of dicarboxylic acids and glycols[94,107,112], as well as higher lactones[108–111]. When the high dilution technique is used (with a mixture of pyridine and ether as solvent), the yield on cyclisation reaches 80%,[109] so that oxidative condensation followed by hydrogenation has been suggested as a method for synthesising exaltolide[108]:



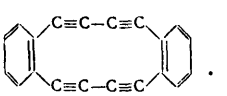
It is interesting that acetylenic macrocyclic lactones possess antibiotic activity[113].

Oxidative condensation has been used for the synthesis of ethers[114,115] of the types

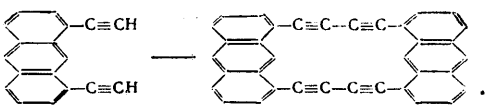


It has also been shown that cyclisation is in principle possible in the oxidative condensation of peptides containing ethynyl groups[116].

The fact that an acetylenic grouping is a "rigid group" plays an important part in the cyclisation of acetylenic compounds[107]. The effect of rigid groups is still greater when the molecule contains aromatic rings. For example, oxidative condensation of *o*-diethynylbenzene under conditions of high dilution gives a 43% yield of the highly strained cyclic molecule[117]†



The value of molecular rigidity is very clearly seen in the cyclisation of 1,8-diethynylanthracene[119]



† A similar type of product is formed also from 9,10-diethynylphenanthrene[118]. It is suggested in this paper[118] that formation of such strained molecules is made possible by an intermediate copper complex containing *o*-diethynyl compounds as ligands (a more detailed discussion of the significance of complex formation in the synthesis of macrocycles will be found in Section 4B).

A yield of 95% is obtained without the use of high dilutions. This result is not unexpected, since the rigidity of the initial molecule, with the ethynyl groups arranged in parallel, greatly diminishes the possibility of polycondensation. In other words, the conditions obtaining here correspond to Stetter's principle[44,45] already considered, according to which synthesis of a macrocyclic compound is facilitated if steric hindrance interferes with formation of a linear polycondensation product‡.

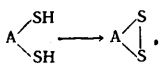
The mechanism of the synthesis of cyclic acetylenes by oxidative condensation has not been studied specially, but it is assumed[107] to be analogous to that established by Klebanskii *et al.*[121] for the polymerisation of linear acetylenes. This mechanism comprises a slow stage of acid dissociation and two rapid stages involving oxidation of the anion to a radical and dimerisation of the radicals:

$$RC{\equiv}CH \rightleftarrows RC{\equiv}C^- + H^+,$$
$$RC{\equiv}C^- + Cu^{2+} \rightarrow RC{\equiv}C^{\cdot} + Cu^+,$$
$$2RC{\equiv}C^{\cdot} \rightarrow RC{\equiv}C{-}C{\equiv}CR.$$

The univalent copper formed in the process is oxidised by air to bivalent copper, so that the process can occur with catalytic quantities of copper salts. In the case of $\alpha\omega$-diynes the resulting biradical $^{\cdot}C{\equiv}C{-}A{-}C{\equiv}C^{\cdot}$ can be stabilised either intramolecularly or intermolecularly with formation of various cyclic and linear products.

### Cyclisation of Dithiols

The synthesis of cyclic disulphides by the oxidation of dithiols



has recently found important uses. Its application to alkane-$\alpha\omega$-dithiols has been studied systematically by Schöberl and Grafie[122]. This method is used in the synthesis of oxytocin and its analogues: first the polypeptide chain is built up, and then cyclisation is carried out, in the course of which the mercapto-groups of two cysteine groupings present in the chain are oxidised with formation of a disulphide bridge (see for example Ref. 12).

We shall not consider in detail the synthesis of porphyrins, since this question has been very fully discussed by Woodward[13], but we will examine isolated examples below. Here it may be pointed out merely that in these syntheses, as in those of azaporphins and phthalocyanines, the effect of rigid groups is of great significance[23], for as a result comparatively high yields of these extremely complicated compounds are obtained without the use of high dilutions. In this connection we may also note the synthesis of furan analogues of porphyrins[123].

Research on the synthesis of macrocyclic peptides and depsipeptides has developed considerably during recent years, in connection with proofs of the structure of several antibiotics, in particular gramicidin S and enniatins. This work lies far beyond the scope of the present review, and has been surveyed in some detail by Shemyakin in a monograph[9] and in a review paper[124]. Here it is relevant to note merely that the cyclisation stage in such syntheses consists in the formation of an amide link under conditions of high dilution, the usual methods of peptide synthesis being used to carry out this reaction, in particular the oldest and simplest of them, interaction of an acid chloride with a peptide having a free amino-group[125].

‡ At first sight this is contradicted by the observation that 1,8-bisbutadiynylanthracene forms the oxidative condensation product in only 17% yield[120]. However, the low yield of the macrocycle in this case is explained by the relative instability of the initial compound.

## 3. DEPOLYMERISATION

Degradation processes in macromolecular compounds with formation of macrocycles may be either reversible or irreversible, the first type being characteristic of heterocyclic compounds containing labile bonds, and the second of alicyclic compounds.

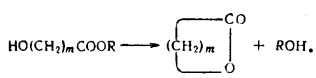
### Reversible Processes

If polymerisation or polycondensation is reversible, we have in general the ternary equilibrium

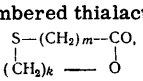
$$\text{polymer} \rightleftarrows \text{linear monomer} \rightleftarrows \text{cyclic monomer}.$$

An example of this type of process is provided by the polymerisation of $\epsilon$-caprolactam, in which the lactam may be in equilibrium with 6-aminohexanoic acid and the polyamide. In the case of a many-membered cyclic monomer (eight-membered ring and larger) the above ternary equilibrium is almost entirely displaced towards the polymer[3]. If, however, the cyclic monomer is continuously removed from the equilibrium mixture, it can be obtained as the sole product. It was in this way that Carothers and his collaborators obtained monomeric and dimeric cyclic anhydrides of higher dicarboxylic acids[126], cyclic esters of glycols and dicarboxylic acids[127,128], and higher lactones[129]. Eight-membered salicylides and similar compounds have been obtained in an analogous manner[130,131]. Depolymerisation occurs on heating in a vacuum the corresponding polymeric anhydrides and polyesters in the presence of substances capable of cleaving the C–O bond (stannous chloride, magnesium chloride, magnesium oxide, etc.), provided that the macrocyclic compound is continuously removed. The patent literature indicates that the metals magnesium[132] and aluminium[133] are the most effective catalysts for the production of oxalactones and cyclic esters of dicarboxylic acids with glycols.

Subsequently Carothers' method of preparing lactones was improved. The process is considerably accelerated if depolymerisation is carried out in glycerol in the presence of a transesterification catalyst (an alkoxide[134,135] or an alkali-metal carboxylate[136]), the lactone distilling off in the glycerol vapour. Collaud[134], who first prepared an ester from glycerol monochlorohydrin and a sodium $\omega$-hydroxyalkanoate, supposed that formation of a macrocyclic lactone involves an intramolecular transesterification§



§ Collaud's method has recently been employed[137] to obtain fifteen- and seventeen-membered thialactones of the type

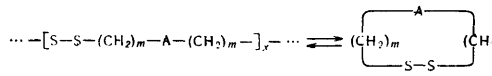


which, like many-membered ketones and lactones, possess a musk odour and strong fixative properties.

Such a change can undoubtedly occur under the reaction conditions, but is also clear that a polyester will then certainly be formed in the mixture: *i.e.* the mechanism of the process should by no means differ substantially from the depolymerisation of polyesters under the conditions suggested by Carothers[23]. The correctness of this view is confirmed by Belov *et al.*[136], who showed that there is no necessity to prepare an ester of the type $HO(CH_2)_mCOOR$ from a hydroxy-acid and glycerol: the previously prepared polyester can be subjected to depolymerisation in glycerol, when the yields exceed 80%, as in Collaud's method.

Higher lactones possessing a musk odour are of considerable interest for the perfumery industry. In this connection simple and practicable processes for obtaining the initial ω-hydroxyalkanoic acids are of great importance. At the present time it is very probably most reasonable to obtain ω-hydroxy-acids and lactones from them on the basis of ααω-tetrachloroalkanes, which are products of the telomerisation of ethylene with carbon tetrachloride[138].

Not long ago a reversible process was described for the depolymerisation of polymeric disulphides[139,140]



This process takes place when the cyclic disulphide is removed together with water vapour; it is accelerated by addition of alkali.

It is interesting that thermal depolymerisation in a vacuum has been used even to obtain macrocyclic chelate compounds of beryllium from the corresponding chelate polymers[141]. Similar changes have recently been effected also by Korshak *et al.*[142], but, what is extremely significant, in dilute solutions instead of a vacuum. The possibility of shifting the equilibrium between polymer and cyclic monomer in favour of the latter by lowering the concentration of the solution has been discussed in detail by Strepikheev[143], who has shown in particular that, with ε-caprolactan at concentrations below 40 g litre$^{-1}$, the equilibrium is almost completely displaced towards the seven-membered ring. As far as I am aware, the above paper[142] provides the first example of the formation of macrocycles under conditions of this kind.

### Synthesis of Macrocyclic Ketones by Ruzicka's Method

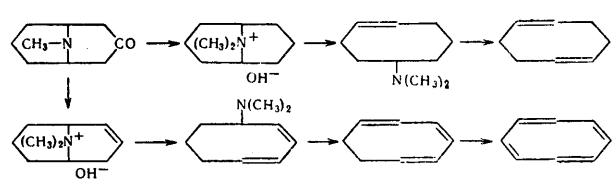
An example of an irreversible degradation process in which a macrocyclic compound is formed is Ruzicka's classical synthesis of macrocyclic ketones[29] by the pyrolysis of salts of higher dicarboxylic acids. In his opinion[144] the formation of cyclic ketones is due to the presence of small amounts of a cyclic form of the salts. However, Stoll and Rouvé showed[145]¶ that the results of pyrolysis do not depend on the method of preparation of the salt: even if during its precipitation the low concentration provided conditions favouring production of a cyclic form, the latter would be converted, owing to the reversibility of the double decomposition and hydrolysis, into the thermodynamically more stable linear form. Formation of a cyclic ketone occurs as a result of several segments of the chain coming together in the course of pyrolysis†, but the main product of pyrolysis is a polyketone. The opinion of Carothers and Hill[147] that in the pyrolysis of salts macrocyclic ketones are formed by reversible depolymerisation of polyketones, resembling what occurs with polyesters and polymeric anhydrides, cannot be regarded as sound. "Formation of cyclic ketones occurs not as a consequence of the depolymerisation of polyketones, as Carothers supposed, but in virtue of the 'depolymerisation' of salts of dicarboxylic acids at the instant of their conversion into ketones"[145].

## 4. SYNTHESES INVOLVING A TRANSANNULAR BOND

The first two groups of methods which we have considered — cyclisation and depolymerisation — are characterised by the fact that the many-membered ring is formed directly from a linear molecule. The characteristics of such a process make it necessary to carry out the reaction under conditions of dilution or with continuous removal of the macrocyclic compound from the equilibrium mixture, which, of course, to some extent limits the practical application of these methods. Restrictions of this type do not exist in syntheses involving a transannular bond, the essence of which is that the macrocycle is formed directly not from a linear molecule, but from a bicyclic or polycyclic system, in the construction of which only the comparatively readily formed three-seven-membered, predominantly five- and six-membered, rings are closed. Scission of the transannular bond, resulting in formation of the macrocycle, is quite often accompanied by the appearance of substituents at the point of cleavage, which enable further reactions to be carried out. A considerable number of syntheses of macrocyclic compounds based on this principle are now known. They can be classified into three groups — (A) scission of one or more bonds in a bi- or poly-cyclic compound, (B) synthesis of a macrocycle with intermediate formation of coordinate bonds, and (C) valency isomerisation.

### A. Scission of One or More Bonds in Bicyclic and Polycyclic Compounds

Classical examples of reactions of this type are Willstätter's syntheses of cyclooctadiene[148-150] and cyclooctatetraene[151,152] from the alkaloid pseudopelletierine (*N*-methylgranatinone), which is present in pomegranate bark:

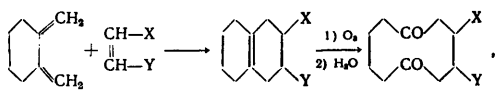


¶ Stoll and Rouvé's paper was published in 1944, but was not discussed in Ziegler's review[23], and therefore it is considered here in some detail. It is especially important because it demonstrates the untenability of the usual view of Ruzicka's method as a cyclisation reaction.

† Such approach may result in the intermediate formation of a cyclic salt, but in the light of modern views of the thermal decomposition of salts of carboxylic acids as passing through a cyclic active complex[146] such a stage must not be regarded as necessary for the production of a cyclic ketone.

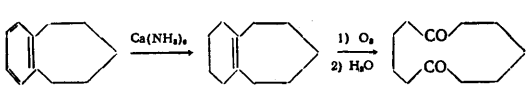
The unusual properties of the hydrocarbons obtained by Willstätter led to doubt being cast on these syntheses for some forty years. It was only in 1948 that Cope and Overberger[153] repeated the synthesis of cyclooctatetraene, and in 1950 Ziegler and Wilms[154] repeated that of cycloocta-1,5-diene, and showed that Willstätter and his collaborators had actually been the first to obtain these compounds. Both the American and the German workers used synthetic pseudopelletierine instead of the natural product for the synthesis, obtaining it in about 50% yield by the Robinson–Schöpf method from glutaraldehyde, methylamine, and acetonedicarboxylic acid. Phenylcyclooctatriene was also obtained from pseudopelletierine[155].

Macrocyclic compounds can be obtained from fused as well as from bridged systems. Thus the synthesis of cyclodecane-1,6-dione by the ozonisation of $\Delta^9$-octahydronaphthalene followed by hydrolysis of the ozonide, proposed by Hückel *et al.*[156], has been used many times by other investigators to obtain cyclodecane derivatives[157,158]. In 1957 Bailey and Golden[159] prepared a series of substituted $\Delta^9$-octahydronaphthalenes by diene synthesis from 1,2-dimethylenecyclohexane, and converted them by ozonolysis into the corresponding cyclodecane derivatives:



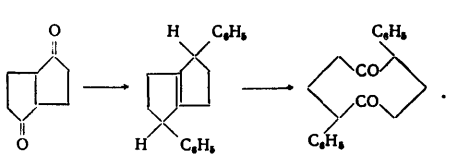
where X = H while Y = $NO_2$, $NHCOCH_3$, $NHCOC_6H_5$, COOH, and X = Y = COOH. The yields at the ozonolysis stage are 40–60%.

In a similar manner Plattner[160] obtained cycloundecane-1,6-dione from benzocycloheptene:

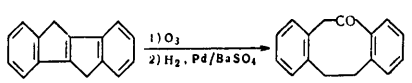


The sesquiterpene alcohol guaiol has been converted by dehydration followed by hydrogenation into 3-isopropyl-6,10-dimethylbicyclo[5,3,0]dec-1(5)-ene, from which the corresponding trialkylated cyclodeca-1,5-diene was obtained by ozonolysis[161].

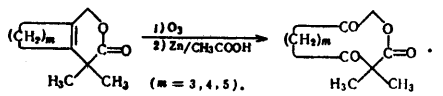
Ozonisation has also been used to obtain cyclooctane derivatives. Wawzonek[162] converted bicyclo[3,3,0]octane-2,6-dione into 2,6-diphenylcyclooctane-1,5-dione according to the scheme



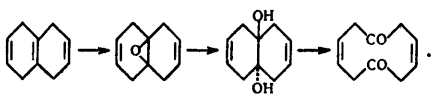
If the ozonide is not decomposed with water, but hydrogenated, a monoketone can be obtained, as has been shown in the case of dibenzocyclooctadienone[163]:



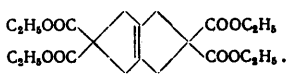
Ozonisation can be used to obtain not only carbocyclic but also heterocyclic compounds. A paper has recently appeared[164] on the synthesis of diketo-lactones of medium ring size by the series of reactions



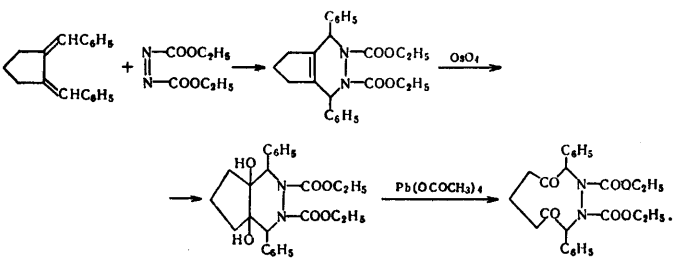
Methods of oxidation other than ozonisation can be used to cleave a C=C double bond, and this is essential if the initial compound contains more than one multiple bond. For example, Grob and Schiess[165] oxidised 1,4,5,8-tetrahydronaphthalene to the corresponding 9(10)-oxide with perbenzoic acid; the product was hydrolysed, and oxidation of the resulting glycol with lead tetraacetate in methanol gave cyclodeca-3,8-diene-1,6-dione:



A similar sequence of reactions has been used to convert indane into cyclonon-7-ene-1,5-dione[166]. Cope and Kagan[167] used performic acid or osmium tetroxide followed by lead tetraacetate to cleave the C=C bond in tetraethyl bicyclo-[3,3,0]oct-1(5)-ene-3,3,7,7-tetracarboxylate

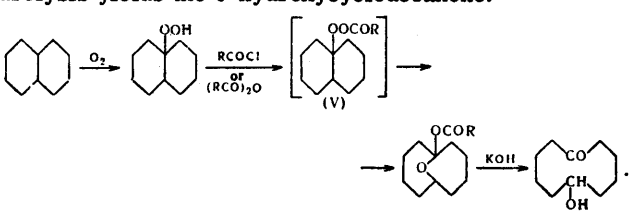


The method of oxidative cleavage of a double bond has also been used to obtain a many-membered heterocycle[168]:



Yields at the two stages of oxidative cleavage are around 60%.

An important reaction for converting decahydronaphthalene into 6-hydroxycyclodecanone was discovered by Griegee[169–172]. Oxidation of decalin with oxygen at 110° gives a hydroperoxide, which rearranges under the influence of an acid anhydride or chloride into an ester of 11-oxabicyclo[4,4,1]undecan-1-ol, and this on alkaline hydrolysis yields the 6-hydroxycyclodecanone:

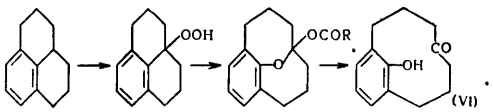


The reaction involves intermediate formation of an unstable hydroperoxide ester (V). The acetate and the benzoate of the hydroperoxide rearrange on being heated, the *p*-nitrobenzoate can be isolated only by working very rapidly, and

the trichloroacetate cannot be isolated at all[171]. In the last two cases the yields of the 11-oxabicyclo[4,4,1]undec-1-yl ester are 68% and 62% respectively based on the hydroperoxide[172]. In spite of the moderate yields of the hydroperoxide (~ 25%)[173], the ready availability of the starting material and the simplicity of the operations make this method of great interest, and it can be used for preparative purposes. A well-known simplification of Criegee's method is to obtain 11-oxabicyclo[4,4,1]undec-1-yl acetate in one stage[173] by the action of oxygen on a mixture of decalin and acetic anhydride, but the yield of the ester is then only 15% based on the decalin which has reacted. Rearrangement of the hydroperoxide to 6-hydroxycyclodecanone can be effected simply by heating it in t-butyl alcohol in the presence of sulphuric acid[173], the yield being 25%.

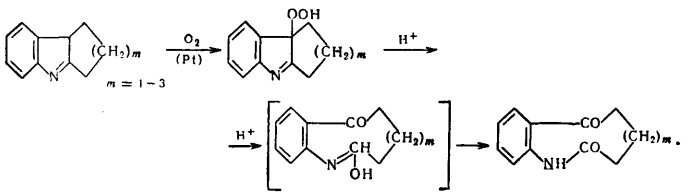
Hexahydroindane behaves similarly to decahydronaphthalene[174]: the hydroperoxide which it forms is converted by *p*-nitrobenzoyl chloride into the 10-oxabicyclo[4,3,1]-dec-1-yl ester (in 58% yield), hydrolysis of which gives a 74% yield of 5-hydroxycyclononanone.

The above process can also be applied to more complicated tri- and tetra-cyclic systems[175-177], for example hexahydrophenalene[175]

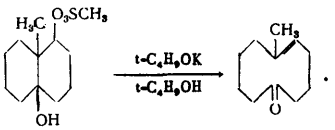



Bicyclic products of the type (VI) are not formed if the aliphatic chain linking the *meta*-position of the benzene ring contains less than seven carbon atoms[177,178].

The method of scission of a C–C bond via a hydroperoxide has been applied also to tetrahydrocarbazole and its cyclic homologues[179]:

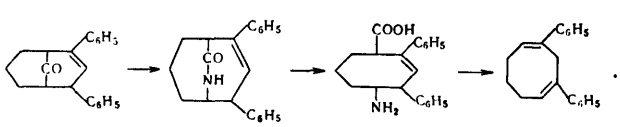



The bicyclic decahydronaphthalene system can be converted into a monocyclic system also by the so-called "fragmentation" reaction, effected by the action of potassium t-butoxide in t-butyl alcohol on methanesulphonic monoesters of 1,3-diols[180]

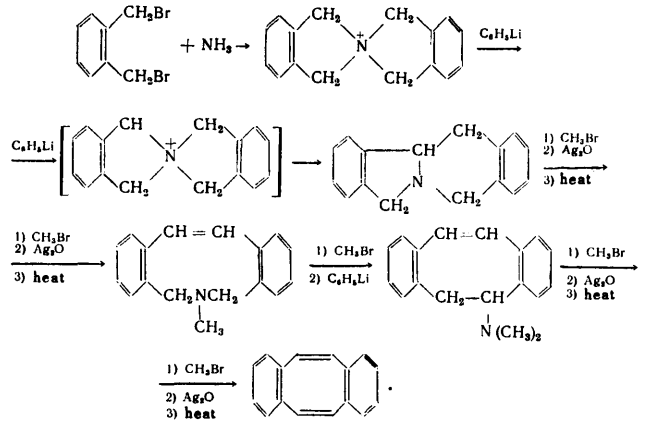



This reaction has found application for the conversion of fused six- and five-membered rings into a nine-membered ring in the synthesis of caryophyllene and isocaryophyllene[181].

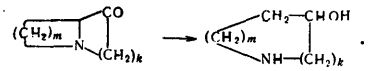
Rupture of the transannular bond can be accomplished in appropriate cases also by a reaction such as the Beckmann rearrangement[182,183]:




Wittig *et al.*[184,185] synthesised eight- and twelve-membered systems fused with benzene rings. The synthesis was based on successive application of the Stevens rearrangement and the Hofmann degradation, as can be seen from the scheme

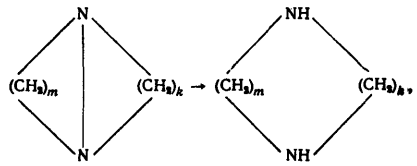



In several cases reductive cleavage of a C–N or an N–N bond is used in the synthesis of many-membered heterocycles. The work of Leonard and his coworkers[186-189] shows repeated applications of the electrochemical reduction of bi- and tri-cyclic amino-ketones, *e.g.* according to the scheme




The initial amino-ketones with $m = 3$, 4 and $k = 2-5$ were obtained by a Dieckmann condensation.

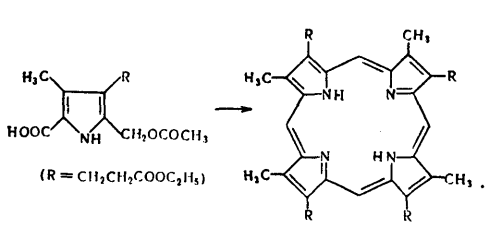
Stetter and Spangenberger[190] described several examples of the cleavage of an N–N bond in bicyclic hydrazines under the influence of Raney nickel:




where $m = k = 3$, $m = k = 4$, and $m = 3$, $k = 4$.

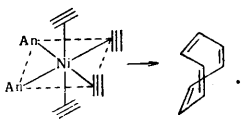
## B. Syntheses with Intermediate Formation of Coordinate Bonds

Coordinate as well as covalent bonds can fill the role of the auxiliary transannular linkage. It has repeatedly been pointed out (see in particular Ref. 23) that, in the synthesis of porphyrins and phthalocyanines, the presence of metal salts may assist formation of a macrocycle in virtue of complex formation. For example, the synthesis of coproporphyrin III in conformity with the accompanying scheme[191] gives a yield of 29%

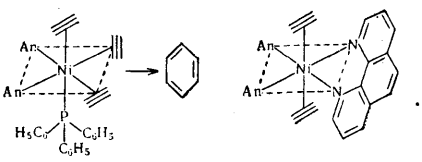


When this cyclisation is carried out in the presence of cobaltous chloride the yield increases to 52%, and, of course, a cobalt complex of the porphyrin is formed, the molecule of which consists of fused five- and six-membered rings. Its conversion into the metalfree porphyrin presents no difficulty. This type of synthesis of macrocyclic ligands, passing through a polycyclic chelate compound as intermediate stage, has been generalised in a recent review by Busch[192]. Below we shall discuss methods of practical importance for obtaining unsaturated hydrocarbons containing eight-, ten-, and twelve-membered rings, with the intermediate formation of coordinate links.

Coordination of four acetylene molecules around a nickel atom is observed in Reppe's synthesis of cyclooctatetraene[193]. Only compounds of bivalent nickel in which the cation is not very firmly bound to the ligands, so that the latter can be replaced by acetylene although it is a weak ligand, can act as catalysts in the Reppe synthesis. The catalysts used are nickel cyanide[193] and various chelate complexes of bivalent nickel (with acetylacetone[194], acetoacetic ester[194], salicylaldehyde[194], salicylaldimine[194,195], and *N*-alkylsalicylaldimines[195]). It is supposed[195] that in the transition state the ligands are arranged at the corners of an octahedron, with the nickel cation at its centre, two of the corners being occupied by anions, and the remaining four corners by acetylene molecules bound as a $\pi$ complex



Formation of the $\pi$ complex facilitates the passage of *sp* hybridisation (the acetylene molecule) into $sp^2$ hybridisation (cyclooctatetraene)[195]. Addition of organic bases, which are able to take the place of acetylene in the transition complex, lowers the yield of cyclooctatetraene[196]. In particular, the latter is not formed at all in the presence of triphenylphosphine[196]. It has been found[195] that under such conditions the acetylene undergoes trimerisation to benzene. This is explained[195] by the $P(C_6H_5)_3$ molecule occupying one corner of the octahedron, while acetylene is coordinated at the three corners remaining vacant. It is significant that in the presence of phenanthroline, which occupies two coordination positions, no reaction at all occurs between the acetylene molecules[195].



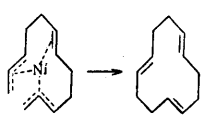
The view is also held[197] that cyclooctatetraene may be formed *via* a complex of cyclobutadiene with the nickel salt, which is unstable in the free state. Experimental data exist which indicate that the conversion of nickel complexes of cyclobutadiene[198] and tetramethylcyclobutadiene[199] into cyclooctatetraene and octamethylcyclooctatetraene respectively, is in principle possible. However, whether the synthesis of cyclooctatetraene does actually pass through a cyclobutadiene stage remains an open question, since the yield of cyclooctatetraene from acetylene is far higher, and reaction occurs under milder conditions, than in the case of synthesis *via* the cyclobutadiene complexes. It may be noted, incidentally, that the above two views are not mutually exclusive, since in the transition state depicted above two acetylene molecules are very conveniently arranged for the formation of cyclobutadiene, and if the latter is formed, it is automatically present as a nickel complex.

In any case, it can be seen from the above that the production of cyclooctatetraene from acetylene involves an auxiliary transannular bond. Substituted cyclooctatetraenes can be obtained similarly from the corresponding substituted acetylenes[200-202].

Besides bivalent nickel compounds, complexes of zerovalent nickel can also be used[202,203] as catalysts for the tetramerisation of acetylene. The Reppe synthesis of cyclooctatetraene gives a high yield (exceeding 70%)[194], and at the present time cyclooctatetraene is the main source for preparing eight-membered carbocyclic systems.

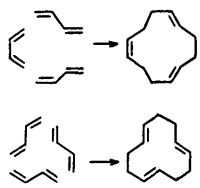
Another important method for obtaining eight-membered rings is the cyclodimerisation of butadiene to cycloocta-1,5-diene by means of zerovalent nickel stabilised as a complex of the type $(R_3P)_2Ni(CO)_2$ (where R represents phenyl[204], phenoxyl[204,205], or methoxyl)[204,205] or else as compounds of general formula $[(C_6H_5)_3X]_4Ni$ (where X = P, As, Sb)[206]. Isoprene[207,208] and penta-1,5-diene[207] can also undergo cyclodimerisation under these conditions.

Cyclodimerisation is accompanied to a greater or lesser extent by cyclotrimerisation, which becomes the main process when $\pi$ complexes of zerovalent nickel with olefins are used[206,209], butadiene being converted in high yields into cyclododeca-1,5,9-triene. This reaction, like the tetramerisation of acetylene, involves formation of a $\pi$ complex of butadiene with nickel. An intermediate $\pi$ complex of nickel with a linear trimer of butadiene has been isolated[210], and then under the action of excess of butadiene or of another substance binding $Ni^0$ into a complex (for example carbon monoxide) converted into cyclododeca-*trans*-1,*trans*-5,*trans*-9-triene



A similar mechanism[211] is suggested for the synthesis of cyclododeca-1,5,9-triene in the presence of mixed organoaluminium catalysts, like that proposed by Ziegler for the polymerisation of olefins. The first stage in this synthesis is the formation of a $\pi$ complex from three molecules of butadiene and a transition metal (chromium or titanium); in this complex three new C–C bonds are established, after which the cyclododecatriene is separated from the metal atom, which can then enter into a new cycle of reactions. Aluminium–titanium catalysts (mixtures of titanium tetrachloride or trichloride with alkylaluminium chlorides) or aluminium–chromium catalysts (mixtures of chromyl chloride with a trialkylaluminium or a dialkylaluminium hydride) are used for the trimerisation of butadiene. Its low-temperature (40°) trimerisation at normal pressure gives in the first case an approximate 90% yield of cyclododeca-*cis*-1,*trans*-5,*trans*-9-triene[212,213]. In the second case a total yield of 90% is obtained of a mixture

comprising 60% of the *trans-trans-trans*-triene and 40% of the *cis-trans-trans*-isomer[212,213]:

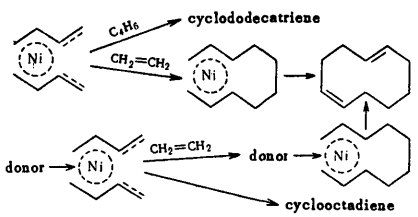


Other 1,3-dienes, in particular isoprene, penta-1,3-diene, and 2,4-dimethylpenta-1,3-diene, can also undergo cyclotrimerisation[213-215].

At the present time cyclodecatrienes are the principal starting materials for the preparation of various twelve-membered carbocyclic compounds and the reaction products. Especial interest attaches to the production from cyclododecatrienes of decane-1,10-dicarboxylic acid and ω-aminolauric acid and its lactam, which are starting materials for the synthesis of valuable polyamides[212,213]. Several papers and patents have been published on the production of these substances (*e.g.* Refs. 216-223).

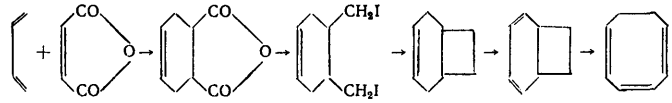
A recent paper[224] has described the preparation in high yields (up to 80%) of cyclodeca-*cis*-1,*trans*-5-diene from butadiene and ethylene by means of zerovalent nickel.

The formation of eight-, ten-, and twelve-membered cycloalkenes is assumed to have a similar mechanism[224]. Interaction of butadiene with nickel yields initially an unstable complex containing two molecules of butadiene per atom of the metal. The action of excess of butadiene on this complex produces cyclododecatriene (*via* a 3 : 1 butadiene–nickel complex). If, however, ethylene is present in the reaction mixture, it combines with the initial complex in preference to butadiene (perhaps steric factors are operative here) and forms cyclodecadiene. When stable complexes of $Ni^0$ with electron-donors (*e.g.* phosphorus compounds) are employed as catalysts, the 3 : 1 complex cannot in general be formed, and cycloocta-1,5-diene is obtained in yields up to 95%; in the presence of ethylene the formation of cyclooctadiene may be accompanied by that of cyclodecadiene (for greater detail see Ref. 224; *cf.* also with the above mechanism for the cyclotetramerisation of acetylene).



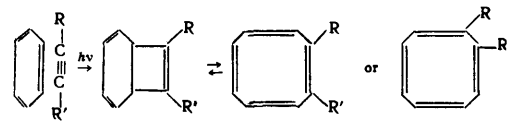

## C. Valency Isomerisation of Cyclic Systems

In this section we shall consider several methods based on the isomerisation of compounds containing normal rings into macrocyclic compounds, where the equilibrium can be displaced to one side or the other depending on the size of the ring. This group now includes a fairly large number of examples of the preparation of unsaturated eight-membered systems from the corresponding mono- and bi-cyclic compounds by the so-called Cope rearrangement. The first work known to the Reviewer in which this method was intentionally used was carried out by Alder and Dortmann[225], who started from butadiene and maleic anhydride and synthesised cycloocta-1,3,5-triene via bicyclo[4,2,0]octa-2,4-diene:




The last stage in the synthesis was based on the work of Cope *et al.*[226], who found that a dynamic equilibrium is established between bicyclo[4,2,0]octa-2,4-diene and cycloocta-1,3,5-triene at 80–100°, with the monocyclic structure predominating (85%). This reaction forms the basis for the preparation of dimethyl cyclooctatrienedicarboxylate from diene synthesis products of cyclobutene-1,2-dicarboxylic ester with butadiene[227,228] and 1,4-dichlorobutadiene[228].

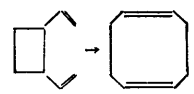
The well-known isomerism of cyclooctatetraene and bicyclo[4,2,0]octa-2,4,7-triene[193,229] is utilised in the preparation of substituted cyclooctatetraenes from photoadducts of benzene and the corresponding acetylenes[230,231]:




where R = R′ = $COOCH_3$, R = $COOCH_3$, R′ = H, R = $C_6H_5$, R′ = H, R = R′ = H.

1,2,3,4-Dibenzocyclooctatetraene can be obtained from the corresponding tetracyclic system[232].

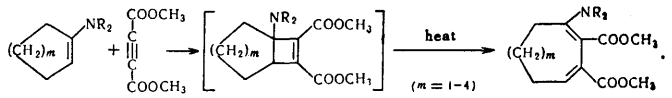
Monocyclic *cis*-1,2-divinyl-cyclobutane and -cyclopropane undergo similar changes, cycloocta-1,5-diene being formed in the first case[233,234]:



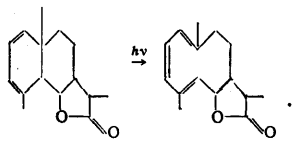
Vogel suggested[235] that the corresponding cycloocta-1,5-dienes, formed together with the normal products of diene synthesis in the thermal dimerisation of butadiene[154,236], chloroprene[237,238], and 2,3-dichlorobutadiene[238] (in the last case as the sole product of dimerisation), are obtained *via* divinylcyclobutane and its chlorinated derivatives. This hypothesis on the mechanism of dimerisation can probably be extended to isoprene and penta-1,3-diene, from the thermal dimerisation products of which Nazarov *et al.*[239,240] isolated the corresponding dimethylcyclooctadienes. In this connection it may be mentioned that 1,5- and 1,6-dimethylcycloocta-1,5-dienes have recently been found among the products of the thermal isomerisation of four-membered cyclic dimers of isoprene[241,242].

It is interesting that in the cases of 1,2-divinylcyclopentane[243] and 1,2-divinylcyclohexane[244] the equilibrium is displaced towards the products containing normal rings, so that an analogous method cannot be used to obtain compounds containing nine- and ten-membered rings.

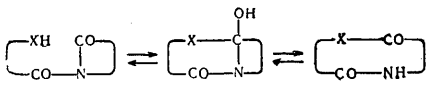
Valency isomerisation has been employed in the synthesis of substituted cycloalka-1,3-dienes via enamines[245]:



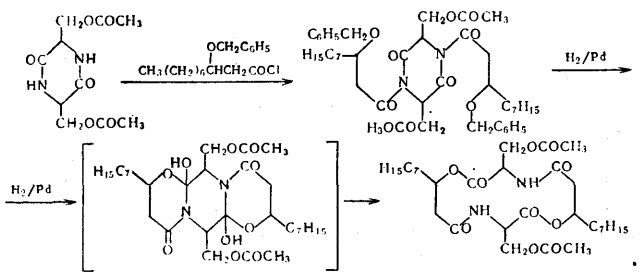
A recently published synthesis of dihydrocostunolide[246] includes as an intermediate step the photolytic conversion of the cyclohexa-1,3-diene into the hexatriene system:



In the opinion of the Reviewer the novel method of synthesising cyclic peptides and depsipeptides discovered by Shemyakin and his coworkers[247-249], which they term aminoacyl and hydroxyacyl insertion in peptide systems, can be included among valency isomerisation methods. It is based on the equilibrium between ω-aminoacyllactams (or ω-hydroxyacyllactams), cyclols, and cyclopeptides (cyclodepsipeptides):

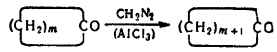


The position of equilibrium depends on the size of the ring[249]. In particular, cyclodepsipeptides are formed beginning with an eleven-membered ring; when ten-membered rings can be obtained, transannular interaction of CO and NH groups is appreciable; but nine-membered rings cannot be obtained at all, the stable form in these cases being the cyclol or an equilibrium mixture of the latter and the ω-hydroxyacyllactam. An important success of this method has been the synthesis of the antibiotic serratamolide. This synthesis is interesting also because it is evidently the first example of the preparation by means of a transannular bond fission of a compound containing a large ring (not a medium ring, as is usual):



## 5. RING ENLARGEMENT AND CONTRACTION

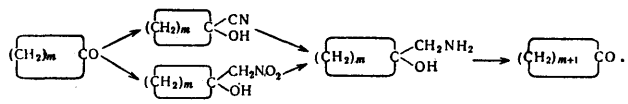
Processes of ring enlargement may yield either a higher cyclic homologue or a compound of a different type. Examples of the first class are the reactions of cyclic ketones with diazomethane, and of the second class the Dem'yanov isomerisation of rings and the Beckmann rearrangement of cyclic ketones. The reaction of cyclic ketones with diazomethane usually gives low yields and produces mixtures of cyclic homologues. Therefore it is little used for preparative purposes[23]. Recently, however, Müller and his collaborators[250-252] have found that in the presence of Friedel-Crafts catalysts the reaction gives high yields (up to 80%) and one product is mainly formed, a ketone containing one cyclic $CH_2$ group more than in the starting material:



This reaction has been verified by the synthesis of ketones from cycloheptanone to cyclopentadecanone. Diazoethane[252,253] and diazopropane[252] give respectively 2-methyl- and 2-ethyl-cycloalkanones, the yields being no lower, and in the case of diazoethane even higher, than with diazomethane.

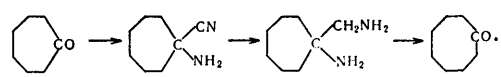
The Dem'yanov rearrangement has been used many times to obtain macrocyclic alcohols and ketones. As early as 1907 Wallach converted aminomethylcycloheptane into cyclooctanol[254]. In 1926 Ruzicka and Brugger[255] prepared cyclononanol in an analogous manner.

Deamination of 1-aminomethylcycloalkanols yields ketones[256]. Since amino-alcohols of the required type are readily obtained from ketones, this procedure enables us to pass from a lower to a higher ketone. This is accomplished by converting the ketone into a cyanohydrin, which gives the amino-alcohol on reduction with hydrogen over platinum oxide[257,258] or with lithium tetrahydroaluminate[216,259]. Another route for obtaining 1-aminomethylcycloalkanols consists in condensation of the ketone with nitromethane followed by electrolytic reduction of the nitromethylcycloalkanol[260]:

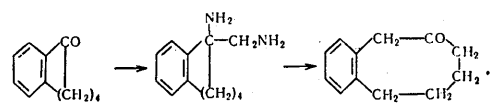


Cyclooctanone[259,261,262], cyclononanone[257,261,262], and cyclotridecanone[216] have been obtained by deamination of the corresponding amino-alcohols.

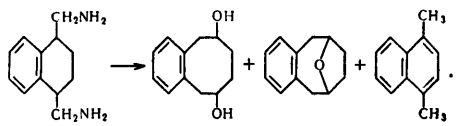
Ketones can be obtained also by the deamination of 1-amino-1-aminomethylcycloalkanes[263], which are readily synthesised from ketones, for example



This reaction has been employed also in the benzocycloalkenone series[264]:

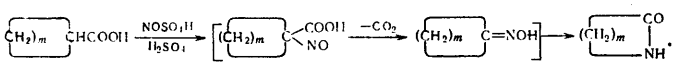


The Dem'yanov rearrangement occurs also with bisaminomethyltetrahydronaphthalene[265], but the reaction is complicated by side-reactions:



Several methods of ring enlargement are specific to the formation of heterocyclic compounds. Thus an important method which allows us to pass from alicyclic to heterocyclic compounds is the Beckmann rearrangement of cycloalkanone oximes[266,267]. This rearrangement has been employed also in the benzocycloalkanone[48,268] and thienocycloalkanone[269] series.

Recently a method has been developed for obtaining lactams by the action of nitrosyl sulphate on cycloalkanecarboxylic acids:

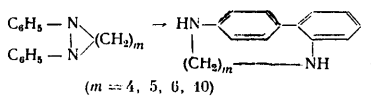


In particular, this method has been used to convert cyclooctanecarboxylic acid into octane-8-lactam[270], and cyclododecane- and cycloundecane-carboxylic acids into the $\omega$-lactams of lauric and undecanoic acids respectively[271].

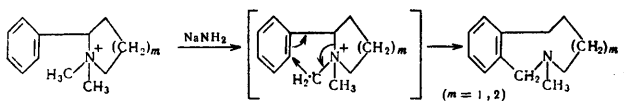
The Schmidt rearrangement is also utilised[272] to obtain macrocyclic lactams.

Cyclic ketones can be converted into many-membered lactones by oxidation with Caro's acid[273] or perbenzoic acid[274].

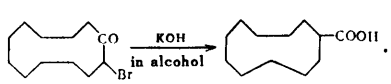
We may note also work on the benzidine rearrangement of *NN'*-polymethylenehydrazobenzenes[275,276]:



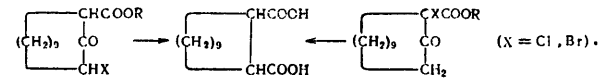
A many-membered heterocycle can be built up also by use of the Sommelet rearrangement[277,278]:



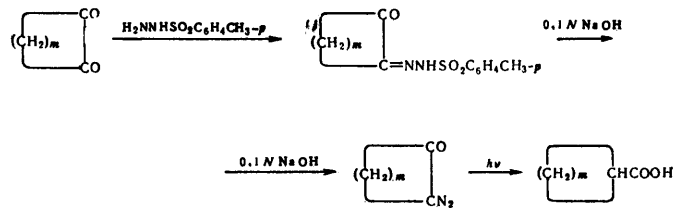
In some cases methods of ring contraction are of preparative interest. As already mentioned, compounds containing a twelve-membered ring have recently become available. In this connection work has been published[279,280] on the conversion of 2-bromocyclododecanone by a Favorsky rearrangement into cycloundecanecarboxylic acid:



Similarly, 1- and 3-halogeno-2-oxocyclododecanecarboxylic esters are converted into cycloundecane-1,2-dicarboxylic acid [formed as a mixture of the (±)- and *meso*-forms][281]:



We may also note ring contraction in cyclic diazo-ketones[282] (Wolff rearrangement). The diazo-ketones are obtained from 1,2-diketones, which are formed by the oxidation of acyloins. These changes are illustrated by the scheme



This reaction has also been utilised in the paracyclophane series[283].

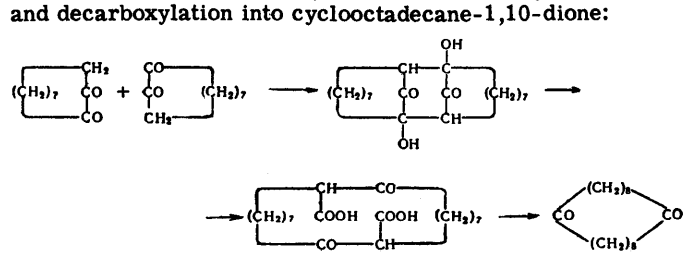
In some cases the conversion of many-membered cyclic bisazo-compounds into tetraphenylcycloalkanes, in which high yields are obtained, may prove useful[284,285].

## 6. COMBINED METHODS

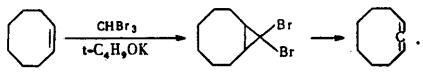
The present section examines methods which strictly belong to none of the above four groups. However, they can be regarded as a combination of two methods, for example the transannular bond method combined with cyclisation or ring enlargement. In all cases to be considered below, the synthesis passes through the stage of a bicyclic or polycyclic compound, but, in contrast to the transannular bond method, these intermediate compounds already contain the macrocycle as a structural unit, obtained either by cyclisation, by the transannular bond method, or by ring enlargement.

Thus Leonard *et al.*[187,188] found eight-membered rings among the bi- and tri-cyclic amino-ketones which they obtained by the Dieckmann reaction; on electrolytic reduction these compounds were converted into twelve-membered cyclic amino-alcohols.

Raphael and Scott[286] obtained a tricyclic compound by the self-condensation of cyclodecane-1,2-dione in the presence of sodium methoxide, and converted it by oxidation and decarboxylation into cyclooctadecane-1,10-dione:

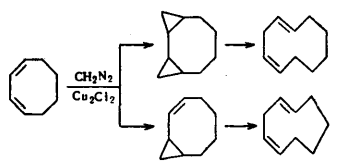


Higher cycloalkenes are converted by the action of dibromocarbene into bicyclic systems, which in the presence of methyllithium[287] or metallic magnesium[288] are transformed into cyclic allenes containing one carbon atom more than in the original cycloalkene, for example

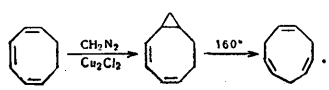



Cyclic dienes having isolated double bonds react at either one or two double bonds depending on the size of the ring[287]

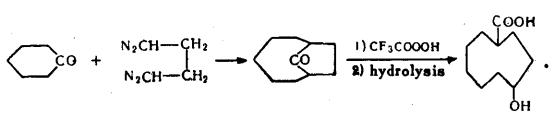
The action of diazomethane on cyclic dienes in the presence of copper(I) chloride gives the corresponding fused bi- and tri-cyclic systems, which at 310–345° rearrange into monocyclic dienes, for example[289]



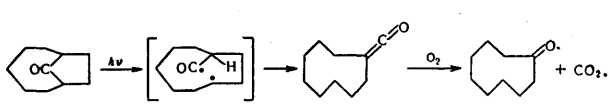

A similar reaction occurs with cyclic trienes[290]



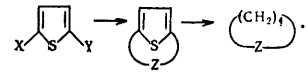

A further method of synthesising compounds containing a medium ring, which is of theoretical interest, is based on a combination of ring enlargement with the transannular bond method[291,292]. Interaction of cyclohexanone and cyclopentanone with 1,4-bisdiazobutane produces bridge ketones, which are then converted into nine- and eight-membered monocyclic compounds, for example




An extremely interesting way of converting a bridge ketone into a monocyclic ketone is photolysis followed by treatment with oxygen[293]:



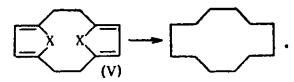

Combined methods include also the novel synthesis of macrocyclic compounds developed by Gol'dfarb and his coworkers[294-307], which is based on the reductive desulphurisation of thiophen derivatives by the action of Raney nickel. The method consists essentially in cyclisation of a long-chain bifunctional thiophen compound to form a bi- or poly-cyclic compound containing the thiophen ring, followed by elimination of sulphur with Raney nickel, resulting in the formation of an alicyclic compound‡:



An important feature of the present method is that thiophen is used not only to build up the skeleton by lengthening the chain by four carbon atoms but also as a "rigid group" to facilitate cyclisation. Furthermore, the great reactivity of the thiophen ring can be utilised for the introduction of substituents§, as well as for effecting the process of cyclisation itself, in which a hydrogen atom of the thiophen ring acts as the second functional group.

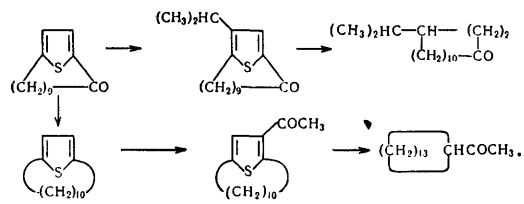
‡ Disregarding for the moment actual methods of effecting the required changes, we can readily imagine the use of various bi- and poly-cyclic systems containing other heterocycles instead of thiophen rings, *e.g.* furan, for the preparation of higher cycloalkane derivatives. However, as far as the Reviewer is aware, no more convenient method of opening a heterocycle for preparative purposes exists other than reductive desulphurisation of thiophen compounds (for greater detail see the reviews in Refs. 308 and 309).

Let us illustrate this by an example: Winberg *et al.*[84] synthesised a tricyclic compound containing two furan rings (V, X = O), and in order to prove its structure converted it into cyclododecane. This was achieved by a four-stage synthesis: the initial compound was subjected to hydrogenolysis over copper chromite, the product acetylated, and the resulting mixture of acetates converted by pyrolysis into a mixture of cycloalkenes, which on hydrogenation over platinum oxide gave the required cyclododecane. If this were a matter of preparing the alicyclic hydrocarbon from the tricyclic system, such a route could hardly be convenient. Nevertheless, if we start from the analogous tricyclic system containing two thiophen rings (V, X = S), conversion into cyclododecane can be accomplished by the action of Raney nickel in one operation.

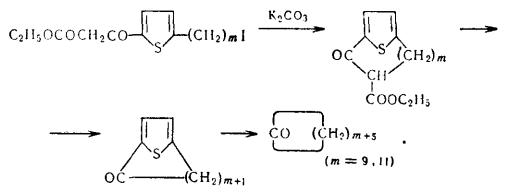



Thiophen can be used in another way for the synthesis of macrocyclic compounds: bifunctional long-chain aliphatic compounds can be obtained by reductive desulphurisation of its derivatives, and the former can then be subjected to cyclisation by one of the known methods. In particular, higher aliphatic dicarboxylic acids and hydroxy-acids have been prepared from thiophen derivatives[310,311], their synthesis by other methods being difficult. However, this second type of use is less specific.

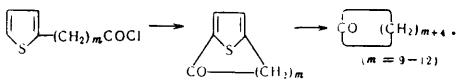
§ This possibility has been realised in the preparation of acetylcyclotetradecane and 4-isopropylcyclotetradecanone[312]:



Cyclisation can be accomplished by Friedel–Crafts acylation[294-296,299-301,305,306], Hunsdiecker intramolecular alkylation[297,298,304], and also acyloin condensation[294,303]. It must be noted, however, that the usual conditions of the acyloin condensation (fused sodium in boiling xylene) are unsuitable for the cyclisation of thiophendicarboxylic esters[294,313]. Success has been achieved[303] only by carrying out the reaction in a mixture of xylene and ether in the presence of a liquid potassium–sodium alloy at 50–60°. Nevertheless, application of the acyloin condensation in the thiophen series is subject to several serious limitations, which impede its use for the preparation of bicyclic systems containing the thiophen ring. In contrast, intramolecular alkylation enables the corresponding bicyclic β-keto--esters containing the thiophen ring to be obtained in high yields (up to 80%), from which the higher cycloalkanones — exaltone and dihydrocivetone — are obtained by ketonic cleavage followed by the action of Raney nickel[297,298,304]:



Intramolecular acylation of ω-thien-2-ylalkanoyl chlorides is especially interesting in that no open-chain bifunctional compound need be built up, since the free 5-position in the thiophen ring acts as the second function. Thus synthesis of the initial compounds is considerably simplified, and the aromatic character of the thiophen ring can be fully exploited. Cyclisation of the higher ω-thien-2--ylalkanoyl chlorides occurs with entirely satisfactory yields (around 60%). From the resulting products, α-cyclothienones, have been obtained cyclotetradecanone, exaltone, cyclohexadecanone, and dihydrocivetone.



Intramolecular acylation is carried out by the high dilution technique in chloroform, with aluminium chloride–ether as condensing agent (for further details see Refs. 306 and 314). Study of the intramolecular acylation of ω-thien--2-ylalkanoyl chlorides reveals a definite effect of the heterogeneity of the medium on the direction of the process, resembling the effect of the surface area of metallic sodium in the case of acyloin condensation. The yields of α-cyclothienone have been found[306] to increase not only with rise in concentration of the condensing agent, which is fully expected, but also at moderate concentrations in the presence of a solid adsorbent, for which purpose aluminium oxide, silica gel, and a product of the incomplete hydrolysis of the aluminium chloride–ether compounds have been used. This effect can be assumed to be due to adsorption of the molecules undergoing cyclisation, and is of general value in various types of cyclisation reaction.

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At the present time the development of synthetic methods makes possible the preparation in quite high yields of the most diverse macrocyclic compounds. Owing, however, to the specific peculiarities and limitations inherent in almost any method of synthesis, the preparation of macrocyclic compounds remains a fairly complicated task. It is difficult to assess the relative value of a particular method, especially in view of the rapid development of this field. Nevertheless, it may be assumed that methods of synthesising macrocyclic compounds "with a transannular bond" will be increasingly developed and applied during the next few years. At present these methods are widely used for obtaining compounds of medium ring size, mainly eight-, ten-, and twelve-membered alicyclic compounds, *i.e.* the particular group of macrocycles which is least readily obtained by cyclisation methods. There can be no doubt, however, that with further development the principle of synthesis with transannular bond, excluding cyclisation with formation of a thermodynamically unfavourable ring, will be extended to the range of large rings[247]. In this connection it is relevant to mention that this principle perhaps underlies the biosynthesis of macrocyclic natural products[315].


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# LUMINESCENCE OF THE RARE-EARTH ELEMENTS AND ITS APPLICATIONS IN ANALYTICAL CHEMISTRY

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