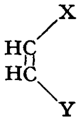
41. *Eight- and Higher-membered Ring Compounds. Part I. General Introduction.*

By Wilson Baker, J. F. W. McOmie, and W. D. Ollis.

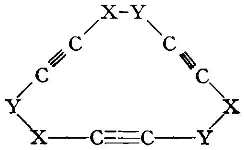
A brief review is given of reactions leading to the formation of large-ring compounds in which ring closure is aided by the device of having the atoms concerned held in a number of rigid groups. Thus, for example, *ortho*-disubstituted benzenes may give rise to eight- (IV), twelve-, and higher-membered rings, *meta*-disubstituted benzenes to ten-membered rings (V), and *para*-disubstituted benzenes to eighteen-membered rings (VI).

The difficulties attending the preparation of many-membered ring compounds from open-chain structures are mainly due to the possibility of rotation about the bonds joining the atoms of which the chains are composed, so that the chance of atoms widely separated along the chain coming within reacting distance becomes rapidly smaller with increasing chain length. Two methods which have been widely used for overcoming this difficulty are the high-dilution technique due to Ziegler (Ziegler, Eberle, and Ohlinger, *Annalen*, 1933, **504**, 94), which minimises the possibility of intermolecular reaction but does not affect the intramolecular cyclisation, and recently the use of the acyloin reaction, where the reactive terminal groups of the chain are restricted in movement by adsorption on the surface of metallic sodium (Prelog, Frenkiel, Kobelt, and Barman, *Helv. Chim. Acta*, 1947, **30**, 1741; Stoll and Hulstkamp, *ibid.*, pp. 1815, 1822; Hansley, U.S.P. 2,226,268; Prelog, *J.*, 1950, 420).

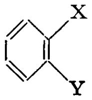
A third method which does not yet appear to have been deliberately exploited for this purpose is to restrict the rotational possibilities by the device of having a number of atoms composing the chain held in the form of a rigid group or groups. The simplest possibility is the formation of an eight-membered cyclic compound by combination of molecules of the *cis*-olefin type, (I), but in practice the possibility of *cis–trans*-isomerisation might frequently raise difficulties. In formulæ (I)—(VI), X and Y represent appropriate uni- or bi-valent radicals, and cases where $X = Y$ are included. Another formally simple type in the aliphatic series is a triple combination of a suitably substituted acetylene $X{-}C{\equiv}C{-}Y$; this linear molecule might give rise to a twelve-membered ring compound (II), but such reactions have not yet been described and we have encountered difficulties in the preparation of suitably substituted acetylenes. The same principle is involved in the dimerisation of butadiene to *cyclo*octadiene (Ziegler and Wilms, *Annalen*, 1950, **567**, 1), and of 2-chlorobutadiene to a dichloro*cyclo*octadiene (Cope and Bailey, *J. Amer. Chem. Soc.*, 1948, **70**, 2305; Cope and Schmitz, *ibid.*, 1950, **72**, 3056), and may also be operative in the polymerisation of acetylene to *cyclo*octatetraene, if vinylacetylene is an intermediate (see Baker, *Endeavour*, 1950, **9**, 36).



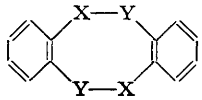
(I.)



(II.)



(III.)

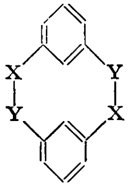


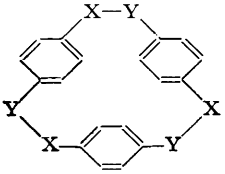
(IV.)

In practice a simpler approach is to secure the required rigidity by using, for example, an *ortho*-disubstituted benzene derivative (III). There are many examples in the literature of the formation of eight-membered ring compounds from such rigid four-membered units, and the formation of larger ring systems containing, for example, twelve-, sixteen-, and higher-membered rings from three, four, and larger numbers of such units is also possible. Recorded cases include the formation of the salicylides, cresotides, sulphonylides, anthranilides, etc., but the simplest are the production of *s*-dibenz*cyclo*octadiene (IV; $X = Y = CH_2$) and *s*-tribenz*cyclo*dodecatriene from *o*-xylylene dibromide by the action of sodium (Baker, Banks, Lyon, and Mann, *J.*, 1945, 27), and the reason why the first two authors undertook the work there described was to investigate the possibility of the formation of large-ring compounds, bearing in mind the considerations which have just been outlined (see footnote, Baker, Banks, Lyon, and Mann, *loc. cit.*).

Other interesting examples of the same kind are to be found in the work of Fieser and Pechet (*J. Amer. Chem. Soc.*, 1946, **68**, 2577) on the synthesis of *s*-dibenz*cyclo*octatetraene, of Rapson *et al.* on the synthesis of tetrabenz*cyclo*octatetraene from 2 : 2′-dibromodiphenyl (*J.*, 1943, 326), of Brown and Farthing (*Nature*, 1949, **164**, 915) who have isolated di-*p*-xylylene from the products of high-temperature pyrosynthesis of *p*-xylene, and of Ziegler and Luttringhaus (*Annalen*, 1934, **511**, 1) on the preparation of a 16-membered cyclic diketone, *m*-$C_6H_4<(CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_2)_2>C_6H_4$-*m*, from *m*-phenylenedipropionitrile.

(V.)





(VI.)

The foregoing ideas may be extended to the *meta*- and *para*-disubstituted aromatic compounds. Thus di-*m*-xylylene, a molecule of type (V) containing a ten-membered ring is readily prepared from *m*-xylylene dibromide and sodium (Baker, McOmie, and Norman, *Chem. and Ind.*, 1950, 77), and *p*-xylylene dibromide similarly yields tri-*p*-xylylene with an eighteen-membered ring, a molecule of novel, essentially triangular type (VI), derived from three linear units (cf. II) (Baker, McOmie, and Miss J. M. Norman, unpublished investigation). Very many variants of the foregoing types of reaction are clearly possible by altering the nature of the reacting groups X and Y, and the object of the work to be described in this series of papers is to investigate the formation, properties, and stereochemistry of large-ring compounds prepared from smaller, rigid assemblies of atoms. Of particular interest is the possibility that compounds of the type (IV) may be able to exist in two stereoisomeric modifications (see Part II, following paper).

The naturally occurring macrocyclic compounds fall into two main types, the simple, large-ring ketones, lactones, etc., and the many-membered cyclic compound which contain a number of rigid aromatic groupings, *e.g.*, certain bisbenzyl*iso*quinoline alkaloids (see Kondo and Tomita, *Arch. Pharm.*, 1936, **274**, 72, where photographs of models are given; Todd *et al.*, *J.*, 1948, 2170; 1949, 2767; 1950, 1606) and *dextro*tubocurarine chloride (King, *J.*, 1948, 265). The porphyrins are probably synthesised in Nature from preformed pyrrole units (Maitland, *Quart. Reviews*, 1950, **4**, 45), but here a central metal atom may also be involved. The synthesis of the sixteen-membered porphyrin ring has, however, been achieved in the laboratory from two almost rigid fragments (see, for example, Gilman, " Organic Chemistry," 2nd Edn., 1942, Vol. II, p. 1282) without, at least deliberate, participation of a polyvalent metal.

The phthalocyanines, although macrocyclic and composed of four rigid groups, are built up around a central metal atom in the form of four fused rings so that, although the rigid group principle is operating, it is not involved in quite the same way.

The following two papers in this series deal with the anhydro-derivatives of salicylic acid and three of the cresotic acids. These compounds contain eight-, twelve-, sixteen-, and twenty-four-membered rings.

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