Newer Developments of the Chemistry of Many-membered Ring Compounds.

CENTENARY LECTURE DELIVERED BEFORE THE CHEMICAL SOCIETY IN LONDON ON FEBRUARY 17TH, 1949.

By V. PRELOG.

I AM able to speak about the newer developments of the chemistry of macrocyclic compounds thanks to the fortunate circumstance that I am working in the Laboratory of organic chemistry at the Institute of Technology in Zürich. In this laboratory the many-membered rings were discovered by L. Ruzicka and the fundamental analytical and synthetical work has been done on this interesting group of compounds. Ruzicka himself lectured on his work before the Chemical Society in London almost exactly 15 years ago.[1] The most important theoretical consequences of these investigations and especially their influence on the so-called strain theory form part of general text-book chemistry to-day. Moreover, the perfume industry could not dispense with the artificial musk-like scents, which became available through this work.

In spite of the wide extent of this field only few laboratories have devoted themselves to the chemistry of many-membered ring compounds. I would like to mention, in addition to the Zürich Laboratory and a connected group led by M. Stoll in Geneva, Carothers, Adams, and Blomquist in America, and Ziegler, Lüttringhaus, and Hunsdiecker in Germany. If I concern myself mostly with the newer work of our own group, it is only on account of restricted time.[2] For the same reason I cannot deal now with the very interesting recent work on many-membered ring peptides, antibiotics, and alkaloids.

The reason why the chemistry of many-membered ring compounds was not more intensively studied lay in their difficult accessibility. In the heroic age, Ruzicka and his co-workers prepared the many-membered ring ketones, which they used as starting materials for other compounds of this group, by dry distillation of the rare-earth salts of dicarboxylic acids.[3] In favourable cases the yields reached a few per cent. The introduction of the dilution principle by K. Ziegler, H. Eberle, and H. Ohlinger[4] did not make the many-membered ring derivatives readily available, since the technique of ring-closure in great dilution is rarely simple. All general procedures for the preparation of macrocyclic compounds had still another important disadvantage. The compounds of medium ring-size, containing 8 to 12 members, could be prepared only in disappointingly low yields of a few tenths per cent.

The introduction of the very advantageous acyloin synthesis,[5] which allows preparation in very good yields of ring compounds having more than 8 members, formed therefore a starting point for new approaches to this field. This synthesis leads from easily accessible dicarboxylic acid esters in a simple way without using great dilutions to macrocyclic acyloins, which can be converted easily into various other cyclic compounds. The following formulæ show a variety of reactions, which were carried out recently :

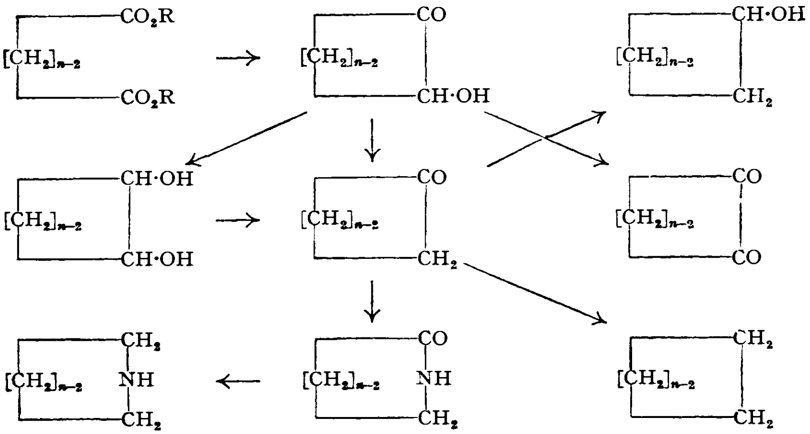
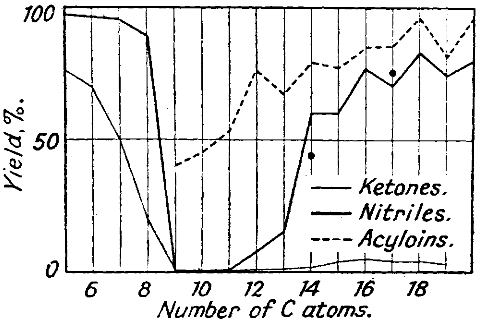


Fig. 1 illustrates the dependence of yield on ring size for the three most important general procedures for the preparation of many-membered ring compounds : the preparation of ring ketones according to Ruzicka, the preparation of imino-nitriles by Ziegler's method, and the acyloin procedure. One can see that it is now possible to obtain ring-compounds of every size in reasonable yield. In this way the field of many-membered ring-compounds became a real playground for the organic chemist. The acyloin procedure leads to the democratisation of this hitherto very aristocratic group of compounds. It is now no more difficult to obtain *cyclo*-decanone than any higher aliphatic ketone.

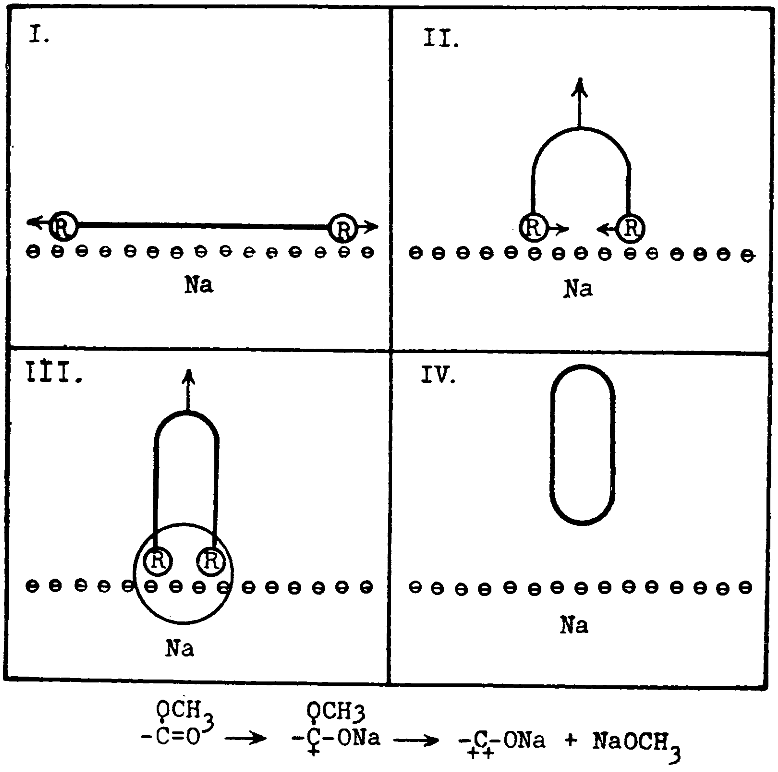
FIG. 1.



A very elegant application of the acyloin synthesis to a macrocyclic compound is exemplified in the synthesis of civetone by M. Stoll, J. Hulstkamp, and A. Rouvé.[6] It was possible to synthesise both *cis*- and *trans*-isomers of civetone and this is the first case of a double bond incorporated in a ring in both *cis*- and *trans*-configuration in known fashion.

The problem of the surprisingly good yields of many-membered ring acyloins obtained from the acyloin synthesis in concentrated solutions is explained by our reaction mechanism shown schematically in Fig. 2.[7] The two electrophilic carbon atoms at the ends of the chain of a dicarboxylic acid ester are first adsorbed by the electron-covered surface of the molten sodium. So far as the flexibility of the carbon chain allows, the electrophilic residues can slide over the metal surface and can thus approach each other. As less energy is necessary for this than for splitting the molecule off the surface, the collisions of the adsorbed molecule with other molecules lead to the approach of the terminal carbon atoms and finally to the ring closure. After the ring closure the molecule no longer possesses electrophilic centres and is therefore no longer bound to the surface.

FIG. 2.



$$\overset{OCH_3}{-C=O} \longrightarrow \overset{OCH_3}{\underset{+}{-C-ONa}} \longrightarrow \underset{++}{-C-ONa} + NaOCH_3$$

The work on many-membered rings was from the beginning carried out with two motives, the one practical—the preparation of musk-like perfumes—and the other theoretical—the investigation of the influence of ring size on the physical and chemical properties. It seemed that this second aim would not have much interest since according to older views the higher unstrained ring homologues of *cyclo*hexane should not differ from it more than the higher aliphatic homologues differ from the lower. In fact *the physical and the chemical properties of the many-membered ring compounds do show a peculiar and unexpected dependence on ring size.*

FIG. 3.

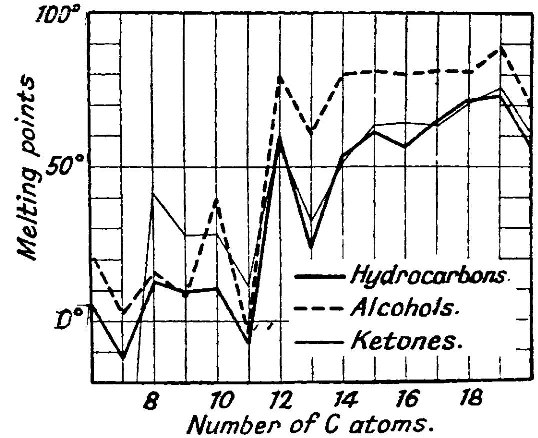
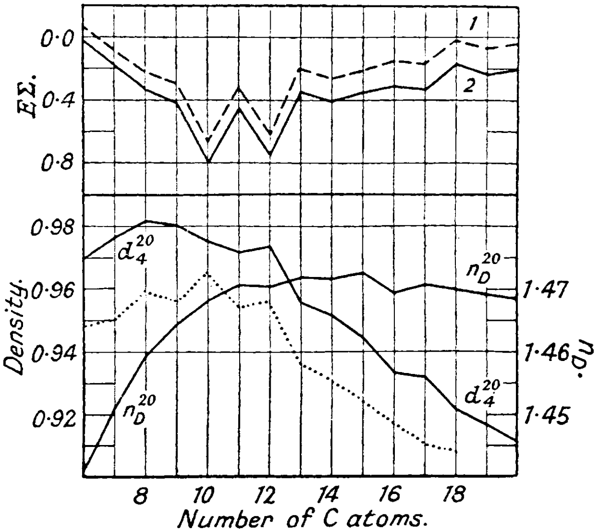


Fig. 3 shows, for example, that the curves of melting point against ring size do not rise steadily as with aliphatic homologues.[8] As no simple explanation of these curves is possible we shall turn rather to consideration of those more readily explicable properties which are not dependent on lattice forces. Such, for example, are the density and the molecular refraction

FIG. 4.



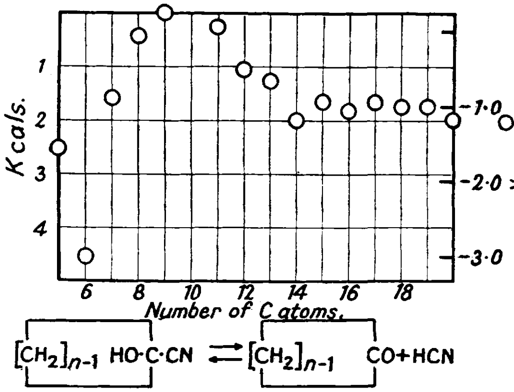
Atomic refractions : curve 1, *Eisenlohr ; curve* 2, *Vogel.*

in the liquid state. Most of the investigated series of alicyclic many-membered ring compounds show a maximum of density and a depression of molecular refraction at medium ring size. In this manner they differ from the aliphatic homologous series, which show a steady increase or decrease of density and no appreciable deviation $E\Sigma$ from the calculated molecular refraction.

Fig. 4 describes the above-mentioned properties as a function of ring size in the series of cyclanol acetates.[8] Cyclanol acetates are specially suitable for such measurements, because the whole series is liquid at room temperature so that no corrections are necessary.

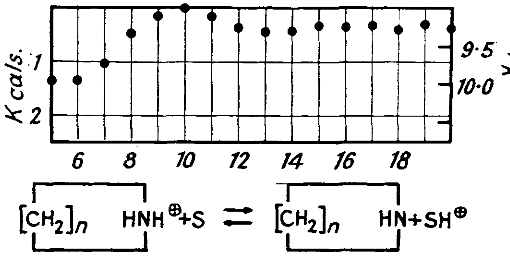
To the extreme values of the physical properties correspond extreme values of the chemical properties of the medium-size ring compounds. As the first example of the chemical properties, the dependence of the equilibrium constants on ring size is shown in Fig. 5 for the reaction between cyclanones and hydrogen cyanide in alcoholic solution.[9] The negative logarithms of the dissociation constants and the free energy of the reaction are plotted against ring size, the influence of which is unexpectedly great. The two extreme values lie on the limits of possible experimental determination. That means that *cyclo*hexanone cyanohydrin scarcely dissociates at all, whereas *cyclo*decanone does not add on hydrogen cyanide. For comparison, the dissociation constant for dioctyl ketone cyanohydrin is given on the right-hand side of the graph.

FIG. 5.



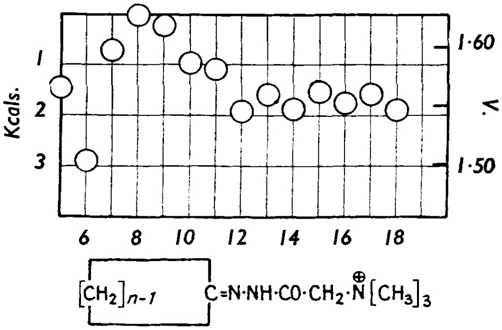
As a further example of the dependence of an equilibrium constant on the ring size we can consider the dissociation constants of polymethylene-imines shown in Fig. 6.[10] We also measured polarographically the half-wave potentials for the cathodic reduction of the Girard-T derivatives of cyclic ketones, which are shown on Fig. 7.[11] In spite of the fact that it is not a reversible reaction, we obtained a shape of curve which shows a dependence of half-wave potentials on ring size very similar to those in the two foregoing examples.

FIG. 6.



The common feature in all these reactions is that at medium-ring size that reaction component is stabilised which contains a more nucleophilic oxygen or nitrogen: for example, ketone is stabilised with respect to cyanohydrin, imine with respect to the corresponding ammonium salt, hydrazone with respect to the reduced form. One possible explanation for this fact is that the nucleophilic centres interact with hydrogens of the polymethylene chain through formation of some kind of intramolecular hydrogen bridge, which is particularly strong if the ring has a medium size. The formation of such intramolecular hydrogen bridges in only possible if we assume a certain constellation of the poly-membered ring. As constellation we define those forms of the molecules which result from free rotation around single bonds, for example, the chair and the boat form of *cyclo*hexane. With respect to stability of form, the poly-membered rings stand in between the rigid small rings and the mobile aliphatic open chains, and therefore these compounds provide an interesting material for studies of the influence of constellation on chemical and physical properties. The following two factors will determine mainly the energy and the probability of a constellation: first, the van der Waals radii of the atoms, which are well illustrated by Stuart models, and secondly, such interactions as are not shown by atomic models—that is, forces not expressed in classical formulæ, for instance, those which restrict rotation around a single bond in aliphatic compounds in contradiction to the views of classical stereochemistry.[12] These forces cause the inequality

FIG. 7.



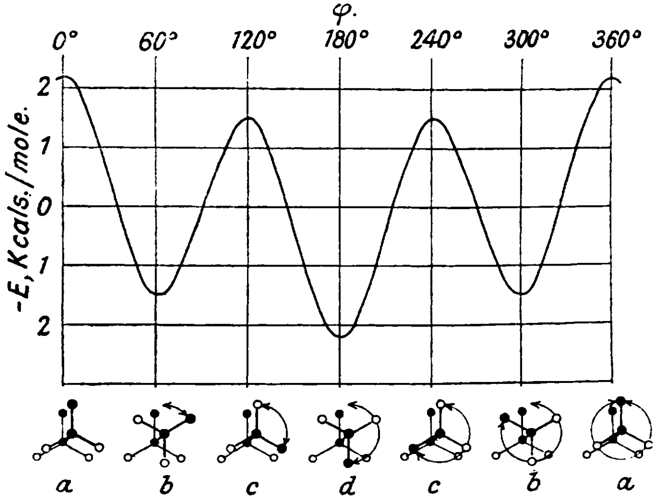
of various constellations of a polymethylene chain from the energetics standpoint. The changes of the potential energy of a chain of four methylene groups around the central C–C bond can be described approximately by the formula [13]

$$E = -1{\cdot}7\cos\phi - 0{\cdot}5\cos\phi \text{ kcals. per mole.}$$

This function is shown together with corresponding configurations in Fig. 8.

Two constellations *b* and *d*, which are separated from each other by energy barriers, are especially favoured. In a normal paraffin hydrocarbon the constellation *d*, which corresponds to the zigzag form of the chain, predominates. In *cyclo*-paraffins the polymethylene chain deviates the more from the constellation *d* the smaller the ring. In *cyclo*pentane and its lower ring homologues the chain is forced by ring strain into the energetically unfavourable constellation *a*. *cyclo*Pentane itself has, according to K. S. Pitzer,[14] a non-planar form because the deformation of the tetrahedral valency angles of the non-planar form is less serious than the unfavourable constellation of the planar form. From this it is understandable that the chair form, which is built from 6 energetically favourable constellations, predominates in *cyclo*hexane over the boat form, in which constellation *b* occurs 4 times and the unfavourable constellation *a* twice.

FIG. 8.



These considerations being transferred to homologous *cyclo*-paraffins and simultaneous account being taken of van der Waals radii, one has the interesting result that medium-sized rings with 8—12 members can only be built from less favourable constellations. In contrast to this, the chains of the higher *cyclo*-paraffins can again be constructed from energetically favourable constellations *b* and *d*. Just as in small rings classical strain and constellation work against each other, so in medium-sized rings van der Waals repulsive forces and constellation are opposed. The medium-sized rings suffer a greater interaction between atoms than in *cyclo*hexane : they are therefore at a higher energy level than unbranched aliphatic compounds.

Maxima and minima in the physical properties of medium-sized ring compounds may be explained in this way, for example, the reduction of electron polarisability and consequently of molecular refraction by the stronger interaction of non-adjacent atoms in the medium-sized rings.

In considering the influence of ring size on the chemical properties, for example, on the dissociation constants of the cyanohydrins, it should be realised that in small-ring ketones the oxygen stands outside the ring. In medium-sized rings we have many possible forms in between the two extreme constellations, which may be termed " O-outside " and " O-inside." Figs. 9 and 10 show such extreme constellations for *cyclo*decanone. The O-outside constellation of medium-sized ring ketones are marked out, first, by a more favourable constellation of the polymethylene chain,* and secondly, by an intramolecular interaction between the carbonyl

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* In the model shown by Fig. 9 we have 6 times the unfavourable constellation *c* and twice the favourable constellation *b*. If the oxygen atom is outside the ring, as in the model shown by Fig. 10, the unfavourable constellation *c* occurs 8 times.

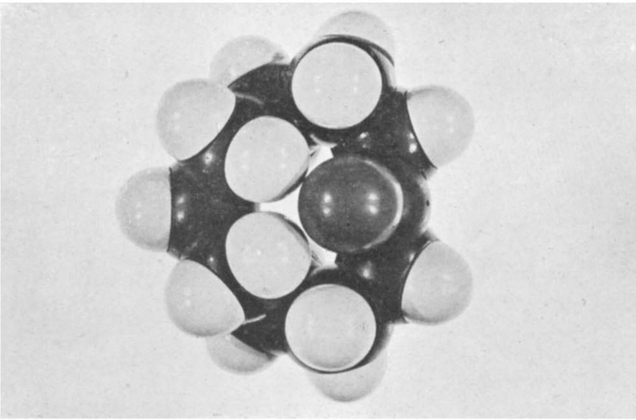


FIG. 9.

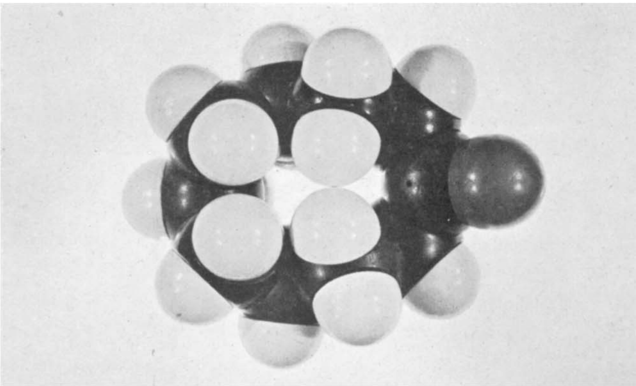


FIG. 10.

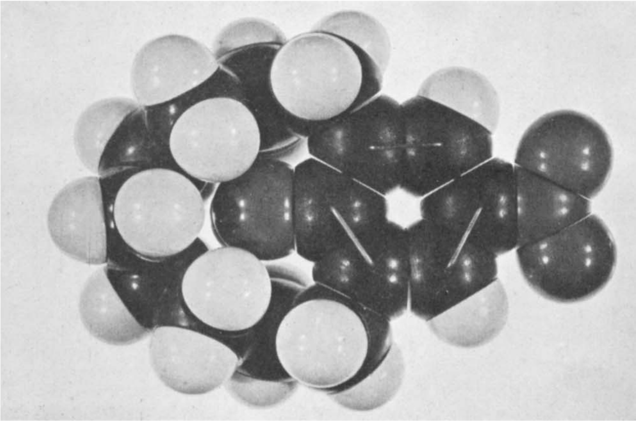


FIG. 11.

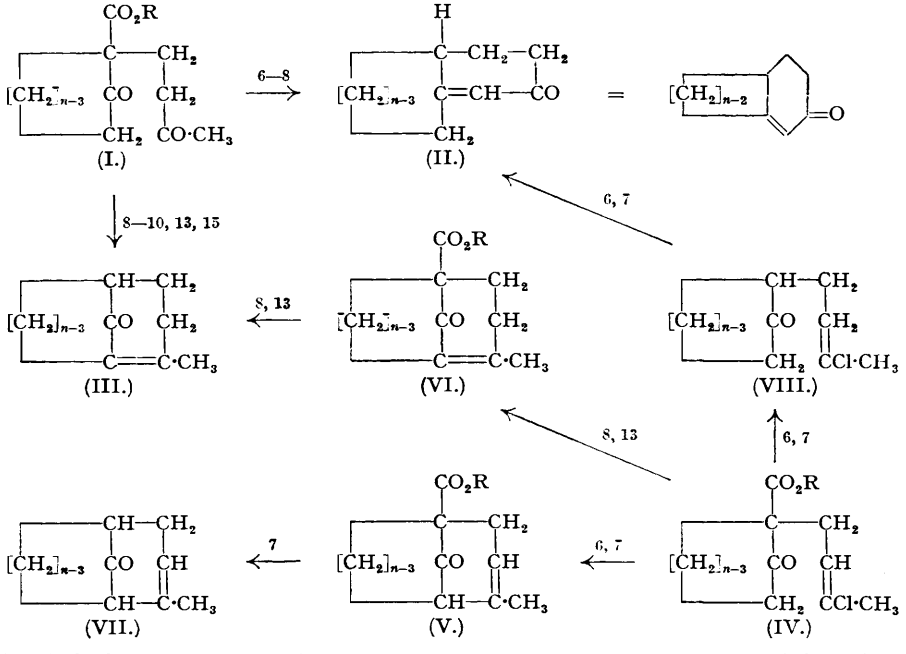
oxygen and the hydrogens of the polymethylene chain; the distance between these atoms is especially small in medium-sized ring ketones. The interaction is stronger in the ketone than in the cyanohydrin and stabilises the former, as was found experimentally. Very similar considerations can be developed for the other reactions mentioned.

In an attempt to prove the consequences of the " O-inside " configuration of cyclanones, Dr. Günthard studied the infra-red absorption spectra. As expected, the frequency of C=O bond-stretching band was smaller with a medium-ring ketone than in *cyclo*hexanone or a large-ring ketone. The following values (in cm.$^{-1}$) were obtained in the liquid state: *cyclo*hexanone 1710, *cyclo*octanone 1692, *cyclo*nonanone 1698, *cyclo*decanone 1694, *cyclo*undecanone 1700, *cyclo*dodecanone 1697, *cyclo*tridecanone 1707.*

In addition to the physical and physicochemical methods of approach, we tried to examine the question of the constellation of many-membered ring compounds by the classical methods of organic chemistry. Assuming that the rate of ring closure is influenced by constellation, it should be possible under favourable conditions to obtain information about the constellation of a monocyclic compound by transforming it into a bicyclic compound. We carried out a series of such experiments and found some facts which deserve brief mention.

Robinson and his co-workers [15] showed that condensation of the *cyclo*hexanonecarboxylic esters with quaternary bases of dimethylaminobutanone (" Mannich base ") gives compounds, which can be simultaneously saponified, decarboxylated, and cyclised to αβ-unsaturated octalones. We obtained analogous products (II) by condensing the cyclic β-keto-carboxylic esters (I) containing a 7- or an 8-membered ring.[16] In the case of the 8-membered ring we isolated a second isomeric αβ-unsaturated ketone (III), in which the carbonyl of the side chain had condensed with the active methylene group in the ring. The two isomers could be separated easily by making use of the fact that the second of them does not give the carbonyl group reactions, for example, does not react with Girard reagent-T. Ultra-violet absorption spectra and Kuhn–Roth oxidation provide evidence for the constitution. The compound with the bicyclic system condensed in the 1 : 2-position has an absorption maximum at a shorter wave-length and gives no acetic acid by oxidation, whereas the isomer with the bicyclic system condensed in the 1 : 3-position gives one molecule of acetic acid by oxidation and absorbs at longer wave-length. Using higher homologues of *cyclo*octanonecarboxylic ester, we got only products of the type (III)

Bredt's Rule.



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* Dr. G. B. B. M. Sutherland, Cambridge, who independently investigated the infra-red spectra of some cyclanones observed in *cyclo*octanone changes in the frequences of the C=O band at about 5·7 μ. as well as of the C–H band at about 1·75 μ., which indicate an intramolecular hydrogen bond.

These experiments permit some definition of the limits of validity of Bredt's rule, which states that in bridged-ring systems a double bond cannot start from a bridgehead. Fundamentally, Bredt's rule expresses the requirement of effective overlap of the *p*-electron orbitals constituting the π-electron orbitals of the double bond. Twisting of the inter-atomic axis in a bridged-ring system is thus the simplest case of that steric hindrance of π-electron resonance which has recently been much investigated in systems containing several conjugated double bonds. Bredt's rule is formally broken by the products (III) of the Robinson reaction containing a 1 : 3-bicyclic system, and it is therefore clear that a double bond may lie at the bridgehead of a bicyclic system if the ring only be large enough.

We investigated this problem more thoroughly by a variant of Robinson's synthesis.[17] We condensed the cyclanone carboxylic esters with γ-chlorocrotyl chloride (1 : 3-dichlorobut-2-ene) instead of with the quaternary salt of the " Mannich-base " and treated the products (IV) with concentrated sulphuric acid according to O. Wichterle.[18] The γ-chlorocrotyl derivatives give under these conditions γ-keto-butyl derivatives, which react further as in Robinson's synthesis but without saponification and decarboxylation. The carbonyl of the β-keto-carboxylic ester is less reactive than in ketones, and only bicyclic compounds condensed in the 1 : 3 position are formed independently of ring size. The compounds (V) from the starting material with 6- or 7-membered rings contain, however, no $\alpha\beta$-unsaturated carbonyl, as shown by ultra-violet absorption spectra, or in other words they obey Bredt's rule. In contrast, the compounds (VI) with 8-membered and higher ring are $\alpha\beta$-unsaturated ketones. Thus the limit of applicability of Bredt's rule lies between the systems with a 7- and an 8-membered ring.

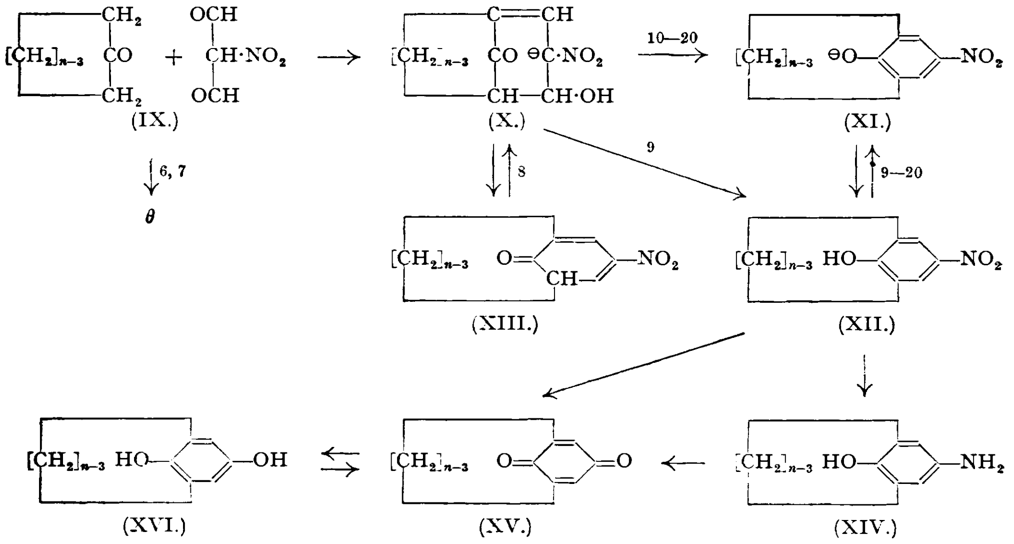
The bicyclic α-keto-carboxylic acids (V) and (VI), which are obtained by the variant of the Robinson synthesis, show an interesting behaviour on decarboxylation. The compound (V) with two 6-membered rings cannot be decarboxylated even under drastic conditions. Similar examples are known from terpene chemistry, for example, camphoronic acid. On the other hand, the analogous acids, (V) with a 7- and (VI) with an 8-membered ring, decarboxylate easily at 240°, whereas the acid (VI) with a 13-membered ring decarboxylates even during the alkaline saponification of the ester. If we assume that an anion at the bridgehead is an intermediate, which must be stabilised by resonance with the carbonyl for the activation energy to be sufficiently low, then we can use these results as a contribution to the knowledge of the validity of Bredt's rule.

I should like to mention that γ-chlorocrotyl carboxylic esters (IV) can be saponified and simultaneously decarboxylated with a mixture of hydrochloric and acetic acids and that treatment of the resulting α-chlorocrotyl ketones (VIII) with sulphuric acid gives the same products (II) as the Robinson synthesis.

Since all experiments showed that the carbonyl in poly-membered ring compounds is feebly reactive, whereas the α-methylene groups are strongly reactive, we tried to condense cyclic ketones with nitromalonic dialdehyde (IX), which gives substituted *p*-nitrophenols easily with aliphatic ketones as was shown by Hill and by Kenner.[19] In fact, the many-membered ring ketones with a more than 8-membered ring gave compounds of the expected formulæ.[20] However, the influence of ring size on the formation of the bicyclic system showed an interesting effect. With 10- and higher-membered ring ketones yellow *p*-nitrophenoxides (XI) were directly obtained, which yielded on acidification *p*-nitrophenols (XII). Ketones with an 8- and a 9-membered ring gave instead colourless condensation products, which contained one molecule of water more than the expected *p*-nitrophenoxides. These products differ in their absorption spectrum from the *p*-nitrophenoxides and probably have the constitution (X).[21] On acidification, the product with a 9-membered ring gives immediately the corresponding *p*-nitrophenol, which can be converted by alkali into the normal *p*-nitrophenoxide. In contrast to this, the primary condensation product which contains an 8-membered ring gives on acidification a compound (XIII) which is tautomeric with the expected *p*-nitrophenol, as could be shown by a thorough investigation. This compound is converted by alkali back into the colourless salt (X), which contains 1 molecule of water more than the *p*-nitrophenoxide. We have here an interesting case of a compound in which the ring strain has overcome the tendency to form an aromatic system. This is in accordance with the model, which shows that the compound (XIII) is much less strained than the *m*-bridged benzene derivative. The *m*-bridged *p*-nitrophenols can serve as starting material for other series of *m*-bridged benzene derivatives, for example, 4-aminophenols (XIV), *p*-benzoquinones (XV), and quinols (XVI).[22]

In the above mentioned *m*-bridged bicyclic compounds the many-membered rings have forms which are very similar to the forms of monocyclic ketones with " O-inside " constellations : this can be seen from the model of a *m*-bridged *p*-nitrophenol, as shown in Fig. 11. Therefore it was interesting to test whether the influence of the medium-sized rings on the chemical properties of the bicyclic compounds was the same as in the monocyclic compounds. The

m-*Bridged Benzene Derivatives.*



aromatic part of the molecule served in these cases as a kind of indicator for the forces inside the ring.

FIG. 12.

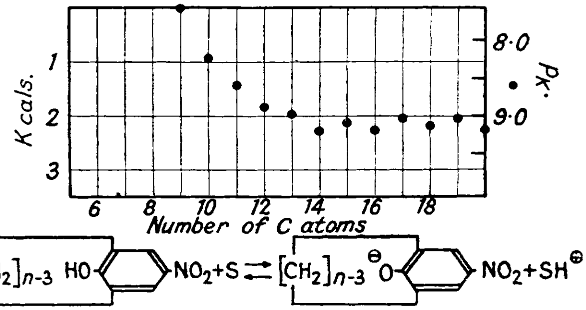
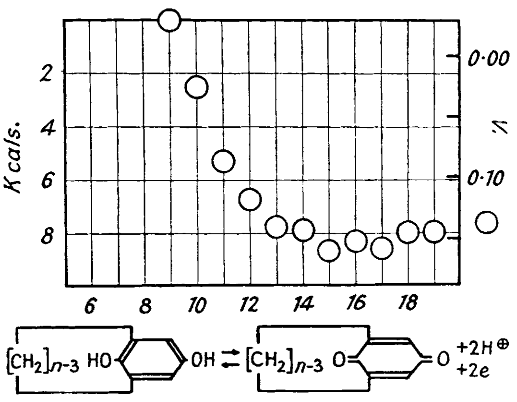


FIG. 13.



We measured the dissociation constants of the *m*-bridged *p*-nitrophenols in 80% Methyl-cellosolve [21] (cf. Fig. 12) and the redox potential of the *m*-bridged *p*-benzoquinones [23] (cf. Fig. 13).

One can see in both cases that the medium-sized rings stabilise the reaction component with the more nucleophilic oxygen, as would be expected on the assumption of the formation of an intramolecular hydrogen bridge.

I believe that the investigations which we have carried out show clearly that *a medium-size ring effect exists which was not predicted by classical chemistry.* I hope that our interpretation of this effect as a consequence of the constellation and intramolecular interactions of atoms across space is not very far from the truth, and that it can be used as a basis for a more exact theory and as a stimulus for further experiments.

The constellation has hitherto often been neglected as a very important factor which influences the reaction equilibria and reaction rates. The advances in physical approach to this problem will perhaps allow the organic chemist to make in the future more valuable contributions from his standpoint than was possible before.

In conclusion, my best thanks for their wholehearted co-operation are due to my younger colleagues P. Barman, L. Frenkiel, O. Häfliger, H. Günthard, W. Ingold, Margrit Kobelt, K. Wiesner, M. M. Wirth, and M. Zimmermann, who performed the laborious and, in experimental details, not always very interesting work. My thanks are due also to Dr. G. W. Kenner for help in the translation of the manuscript.

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[6] *Ibid.*, 1948, **31**, 543.

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[19] Cf. E. C. S. Jones and J. Kenner, *J.*, 1931, 1849.

[20] V. Prelog and K. Wiesner, *Helv. Chim. Acta*, 1947, **30**, 1465.

[21] V. Prelog, K. Wiesner, W. Ingold, and O. Häfliger, *ibid.*, 1948, **31**, 1325.

[22] V. Prelog and K. Wiesner, *ibid.*, p. 870.

[23] V. Prelog, O. Häfliger, and K. Wiesner, *ibid.*, p. 877.