BREDT'S RULE OF DOUBLE BONDS IN ATOMIC-BRIDGED-RING STRUCTURES

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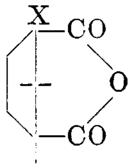
I. INTRODUCTION

Bredt's rule is a qualitative generalization which describes structural limitations in bridged-ring compounds. From steric considerations Bredt concluded that certain bicyclic atomic-bridged-ring structures with a carbon–carbon double bond at a bridgehead atom should not be capable of existence. This rule has been useful in the determination of structure for terpene-like compounds and in the interpretation of reactions of bridged-ring compounds.

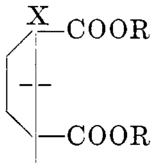
This review covers the literature on Bredt's rule from 1902 through May, 1950. Some work prior to 1902, which has been reinterpreted in terms of the rule, has been included. The examples described are ones in which the rule is referred to explicitly or implicitly, together with a few in which it can be used in interpreting the work reported. The literature has not been searched exhaustively but sufficient examples have been collected to illustrate the major points in the use of the rule.

II. ORIGIN OF BREDT'S RULE

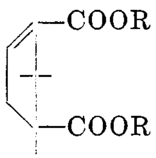
In 1902, Bredt, Houben, and Levy (39) compared the relative ease of dehydrohalogenating α-halocamphoric acid derivatives (I and II). It had previously been observed (12, 39) that α-bromocamphoric acid anhydride (I) was quite stable toward the removal of hydrogen bromide, being unchanged after heating with quinoline for 48 hr. It was found, however, that if the anhydride linkage was opened by conversion to the phenyl ester (II) the removal of hydrogen halide occurred readily to form IV. They further found that the unsaturated acid III failed to form anhydride V, while the corresponding saturated compound readily cyclized. When dehydration of III was forced by distillation at atmospheric pressure there was obtained the anhydride (VI) of the isomeric acid, isodehydrocamphoric acid, having the double bond in another position. It was concluded that III cannot exist in the form of its monomeric anhydride, and Bredt offered the explanation that the hindrance of reactions leading to V was due to the stereochemical nature of these compounds.



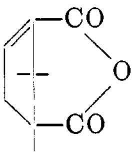
I[1]: X = Cl or Br



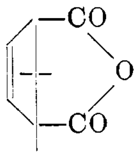
II: R = C_6H_5
X = Br



III: R = H
IV: R = C_6H_5



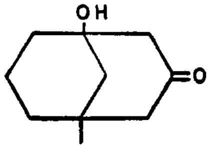
V



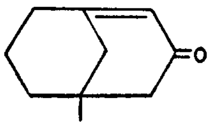
VI

As an explanation for the formation of tricyclic derivatives upon the dehydration of isoborneol and of camphenilic acid (*cf.* page 237), Wagner and Brykner (177) in 1903 suggested that, because of stereochemical limitations, the formation of a double bond at a carbon atom common to two pentamethylene rings is hindered.

Rabe (132) in 1908 pointed out the extraordinary resistance of the β-hydroxyketone VII to dehydration (page 235). He explained this stability on steric grounds: "... the bicyclic system offers great resistance to the formation of a double bond in the [1,2-] position" (as in VIII). He did not mention the previous papers, although they had already been referred to by other workers (111).



VII



VIII

III. STATEMENT OF BREDT'S RULE

In the original reference (39) Bredt's rule was not stated formally. It was developed over a period of time in later investigations, particularly those of

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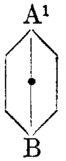
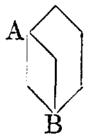
[1] Many of the structural formulas have been drawn with a short line or with Me to indicate a methyl group; a heavy dot as used in the left-hand formula on page 222 represents a methylene bridge.

Bredt and coworkers. In considering specific structures they have indicated in a general way the type of compound in which, according to the rule, a double bond cannot occur, although no single discussion has covered all of the important features of the rule. Bredt's (44) statement of the rule in 1924 is typical of those which have been given: "On the basis of our conceptions of the positions of atoms in space, in the systems of the camphane and pinane series, as well as in similarly constituted compounds, a carbon double bond cannot occur at the branching positions A and B of the carbon bridge (the bridgeheads)."





Since it is inherently a qualitative rule, any simple statement will be indefinite about the borderline area. For the purpose of this discussion the rule may be stated as follows:

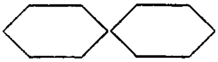
> In polycyclic systems having atomic bridges, the existence of a compound having a carbon–carbon or carbon–nitrogen double bond at a bridgehead position is not possible, except when the rings are large, because of the strain which would be introduced in its formation by the distortion of bond angles and/or distances. As a corollary, reactions which should lead to such compounds will be hindered or will give products having other structures.

IV. Nomenclature and Scope of Bredt's Rule

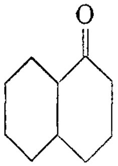
For a typical atomic-bridged-ring compound such as camphor (XIII) the molecule may be considered to be made up of a ring which is spanned by a "bridge" of one or more atoms. The atoms of the large ring to which the bridge is attached (at positions 1 and 4 in XIII) are the bridgehead atoms and Bredt's rule applies to the stereochemistry of these bridgeheads. The concept of a bridge thus focuses attention on the large peripheral six-membered ring of the conventional planar projection, although for nomenclature XIII is regarded as a bicyclic structure made up of two contiguous five-membered rings.

A. BICYCLIC SYSTEMS

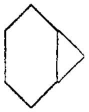
Bicyclic systems can be grouped into the types illustrated by formulas XI, XIIa, XIIb, and XIII. As far as Bredt's rule is concerned the nomenclature problem is to describe the kind of structure in which a bridgehead double bond is sterically improbable and to be consistent in stating and using the rule. According to nomenclature conventions (115) bicyclo $[x.y.z]$ compounds are named in such a way that the numbers in the brackets are in decreasing order: i.e., $x \geqslant y \geqslant z$. Bredt's rule is regarded as applying only to structures having atomic bridges, i.e., to bicyclo $[x.y.z]$ compounds in which $x \geqslant y \geqslant z \neq 0$. Structures having a double bond at an atom common to two fused rings ($z = 0$), for example, the enol form of α-decalone XIIa (3d) or similar ring structures (139), are considered outside the scope of the rule. Those small valence-bridged-ring (fused-ring) structures having $z = 0$ in which a double bond at a carbon atom common to two rings would cause great strain—for example, XIIb—might be covered by other rules analogous to Bredt's rule. Nomenclature systems (3a, 43, 109, 115) differ in what is meant by the term "bridged-ring" and consequently the meaning of the term may be ambiguous. To avoid confusion the term "atomic-bridged-ring" is ordinarily used in this review; when the shorter term "bridged-ring" is used, it is intended to mean only structures having atomic bridges.



XI
spiro
(one atom
in common)

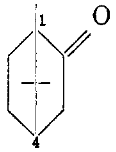


XIIa



XIIb

fused or
valence-bridged
(two atoms in common)



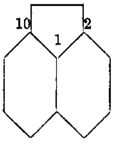
XIII
bridged or
atomic-bridged
(three or more
atoms in common)

Bredt's rule applies to structures having double bonds involving either carbon or nitrogen but it is not certain whether it applies to a carbon–sulfur double bond (page 255). The rule apparently has not been used with other hetero atoms. It has been applied to systems in which the double bond is part of an aromatic ring. In such compounds, which effectively contain two bridgehead double bonds, the requirements of planarity and presumably the strain will be greater than with only one, but the resonance stabilization of the aromatic ring may tend to compensate for this (compare page 242). Hetero atoms in positions removed from the bridgehead apparently have no special influence.

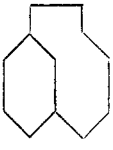
In discussing the different possible positions for a substituent or a double bond in a bicyclo[$x.y.z$] compound—for example, bicyclo[3.2.1]octane—it is convenient to refer to a particular "branch" of the bicyclic system as the [3], the [2], or the [1] branch. A term S, defined by $S = x + y + z$, is used in discussing the total ring size of a bicyclic system; thus, in bicyclo[3.2.1]octane, $S = 3 + 2 + 1 = 6$.

B. TRICYCLIC SYSTEMS

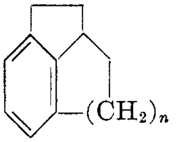
Many tricyclic systems in which all of the rings are not mutually contiguous can be treated as substituted bicyclic compounds. With three mutually contiguous rings, however, there may be some question about whether the rule applies to certain structures, since the criterion of the number of atoms in common needs qualification. Bredt (43) regarded perhydroacenaphthene (XIV) and similarly constituted structures as bridged-ring, considering, for example, C_1 as a bridge across the eleven-membered ring between C_2 and C_{10}, while Patterson (115) considered XIV to be fused-ring, resulting from three ortho fusions (two atoms in common) among the three rings. Hückel (77b) included the unknown ring system XVa in a discussion of Bredt's rule and related topics. Compounds of this type with bridgehead double bonds are known where the rings are larger, for example, tetrahydroacenaphthene (XVb), and models do not indicate these to be unreasonably strained. The ring size of course is important here as with bicyclic structures, although the critical value of a term analogous to S may be different from the value of S for a bicyclic system (*cf.* pages 223, 226). An approximate criterion of whether the rule permits or forbids a bridgehead double bond in a tricyclic structure such as XIV or XVb is to consider the smallest bicyclic analog from which it can be regarded as being derived by incorporation of an additional bond or bridge. A comparison of XIV with bicyclo[6.3.1]dodecane (XVd: $S = 10$, page 223), in which because of ring size Bredt's rule allows a bridgehead double bond, suggests that because of the ring size the rule should not prohibit such a bond in XIV. It seems logical that the rule be used to describe the impossibility of a bridgehead double bond in smaller-ring compounds like XIV even though each pair of rings has only two atoms in common. Such structures have many of the steric characteristics of their bicyclic analogs, and the presence of the additional bond or bridge would not be expected to reduce the amount of strain. Thus a compound having structure XVc (116), which might be derived from bicyclo[3.2.1]-5-octene by adding a carbon bridge, is regarded as prohibited by Bredt's rule (page 224). According to the rule a compound with the structure bicyclo[3.2.1]-5-octene ($S = 6$) is impossible, and the additional C_3–C_8 carbon bridge would hardly make the double bond less strained.



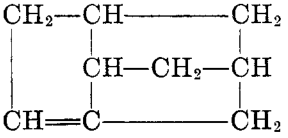
XIV
Perhydroacenaphthene



XVd



XVa: $n = 1$
XVb: $n = 2$



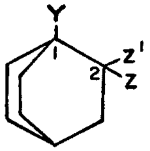
$$\begin{array}{ccccc} CH_2 & - & CH & ——— & CH_2 \\ | & & | & & | \\ | & & CH & -CH_2- & CH \\ | & & | & & | \\ CH & = & C & ——— & CH_2 \end{array}$$

XVc

V. Stereochemistry of Bredt's Rule

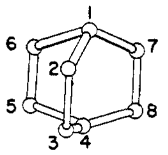
The condition which Bredt emphasized is the strain which would be present in a compound having both a small atomic-bridged-ring system and a bridgehead double bond. The rule has often been used in making a choice between structures suggested for a chemical compound. In other instances the hindrance of a reaction has been explained by applying the rule to the expected product or to probable reaction intermediates. This type of steric hindrance can occur (*a*) with ring-closure reactions of unsaturated cyclic compounds which would form a bridged-ring system, and (*b*) in elimination or displacement reactions of bridged-ring compounds having substituents at or adjacent to the bridgehead position.

The cause of the hindrance in the ring closures can be regarded as the inability of the reactive groups to come within bond-forming distance of each other. Bredt (33) described the two carboxyl groups in III as being in positions intermediate between the *cis* and *trans* positions and used the term "*meso-trans*" to describe their relationship. Elimination or displacement reactions of bridged-ring derivatives may tend to give intermediate bridgehead carbonium ions, carbanions, or free radicals. In addition to their other special structural features, allylic- or benzylic-type bridgehead intermediates lack the resonance stabilization which is present with their open-chain or monocyclic counterparts (page 230), and consequently reactions which should involve them may be hindered. The groups which would participate in the elimination reaction may be so arranged that a *trans* elimination (54) is not facilitated, as in IX, where neither Z nor Z′ is *trans* to the bridgehead substituent Y. Elimination is hindered (54) in certain structures in which the atoms involved are not in favorable positions, but there appears to be no basis for deciding the relative importance of this effect and the impossibility of the formation of the olefinic product which would result from elimination. The decarboxylation of β-keto acids (page 246) as well as some *cis* eliminations (2a) are considered to involve cyclic intermediates. While substituents at C_2 (IX) seem reasonably close to Y for the formation of such quasi-rings, the redistribution of the electrons to the 1,2-position to form an actual or a transient double bond as required for elimination or for enolization (page 249) would be hindered, according to Bredt's rule.

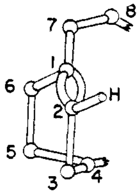


IX

The prohibitive strain which would be present in a small atomic-bridged-ring structure having a bridgehead double bond can be illustrated by means of models. The cyclohexane ring C_1–C_6 in Xa has bond directions at C_1 and at C_4 which will accommodate the C_7–C_8 bridge without appreciable strain. With a carbon–carbon double bond at C_1–C_2, however, the preferred bond direction from C_1 is no longer one which will permit a two-membered bridge to reach C_4 without considerable difficulty. Carbon atoms C_1 and C_2 and the four atoms attached (C_3, C_6, C_7, and H) all must lie in a common plane if the system is to be strainless. Woodward and Kovach (201) considered that Bredt's rule follows as a simple corollary from this principle as applied to small bicyclic systems. Freudenberg (66) interpreted Bredt's rule as meaning that the two substituents attached to one of the carbon atoms of a carbon–carbon double bond cannot lie on the same "side" of the double bond, i.e., the same side of the plane through C_1 and C_2 suggested by the curved bonds in Xb. Prelog (123) interpreted the rule as describing the conditions necessary for effective overlap of the *p*-electron orbitals constituting the π-bond of the double bond (*cf.* page 227). If the unsaturated bridged-ring structure pictured by Xb were to be formed by closing the C_4—C_8 bond, a large amount of energy would be required in distorting bond angles and/or distances and the resulting structure would be highly strained. Bartlett and Knox (20) estimated that such a structure with a bridgehead double bond would be less stable than the isomer with a C_2–C_3 double bond by approximately 22.5 kcal. per mole and thus the probability of the existence of the former is quite low. The 1,2-double bond and the small bridged-ring system are thus mutually exclusive.



Xa



Xb

A long chain of carbon atoms from C_1 is able to reach C_4 without great strain, even with the C_1–C_2 double bond (Xb); hence the rule does not prohibit a bridgehead double bond in bridged rings of unlimited size. The rule, however, does not divide ring sizes sharply into those where a bridgehead double bond is possible and those where it is not possible, since insufficient experimental data have been obtained in the borderline area. There will be intermediate ring sizes, different bridgehead positions with a given ring size, or transient reaction intermediates where the possibility of a bridgehead double bond cannot be predicted. According to ball-and-peg models, in a bicyclo[$x.y.z$]alkene ($x \geqslant y \geqslant z \neq 0$) structures with a double bond at a bridgehead can be made strainlessly when $x + y + z = S = 11$. Many structures with a bridgehead double bond can be formed with little strain when $S = 10$, some even with $S = 9$, but with $S = 8$ the strain is quite large. Bredt (34) concluded that bicyclo[4.4.1]-1,6-undecadiene ($S = 9$), having a double bond at each bridgehead in the [4] branches, can be constructed from models almost strainlessly, while considerable strain is present when a double bond lies in the [1] branch, as in bicyclo[4.4.1]-11-undecene (compare Section VI, C, page 248). From a study of bicyclo[x.3.1]alkenones Prelog and coworkers (123, 124, 127) (table 1) concluded that $x = 5$ ($S = 9$) represents the smallest ring size where a bridgehead double bond can occur in an isolable compound. The conclusions from models thus appear to correspond reasonably well with the observed structures, i.e., with $S = 9$ a bridgehead double bond is possible. The tentative upper limit to the ring size for which the rule forbids such double bonds in isolable compounds is $S = 8$. For a transient reaction intermediate such as is thought to occur in the decarboxylation of β-keto acids this limit is probably lower, tentatively at $S = 6$ (page 248).

Attachment at C_2 or at C_6 in Xb to form a bicyclo[4.n.0]alkene valence-bridged-ring (fused-ring) structure, while requiring some distortion of bond angles when closing a small ring, does not involve such a drastic change of bond direction as in forming a bicyclo[3.n.1]alkene or a bicyclo[2.n.2]alkene bridged-ring structure. These fused-ring structures are considered to be outside the scope of Bredt's rule.

TABLE 1

Formation of bicyclic compounds by intramolecular aldol condensation

(Prelog and coworkers)

STARTING MATERIAL		PRODUCT				REFERENCE
Structure	n	Bridged (B) or fused (F)	Bicyclic system [$x.y.z.$]	S $(x+y+z)$	Double bond(s)	
LXX(a)	3	F	[4.4.0]		α,β	(127)
	4	F	[5.4.0]		α,β	(127)
	5	Mixture				
		F	[6.4.0]		α,β	(127)
		B	[5.3.1]	9	α,β	(127)
	6	B	[6.3.1]	10	α,β	(127)
	7	B	[7.3.1]	11	α,β	(127)
	12	B	[12.3.1]	16	α,β	(127)
LXXIII(b)	3	B(c)	[3.3.1]	7	β,γ	(124)
	4	B(d)	[4.3.1]	8	β,γ	(124)
	5	B(d)	[5.3.1]	9	α,β	(124)
	10	B(e)	[10.3.1]	14	α,β	(124)
LXXVIa(f)	3	F	[4.4.0]		Aromatic	(125)
	4	F	[5.4.0]		Aromatic	(125)
	5	B	[5.3.1]	9	Aromatic	(125)
	6	B	[6.3.1]	10	Aromatic	(125)
	10	B	[10.3.1]	14	Aromatic	(130)
	12	B	[12.3.1]	16	Aromatic	(125)

(a) Decarboxylation occurred in condensation, yielding a bicyclic ketone.
(b) Product was a β-keto ester.
(c) The β-keto acid was not decarboxylated on heating with quinoline at 240°C.
(d) Decarboxylation of the β-keto acid occurred on heating with quinoline at 240°C.
(e) Decarboxylation occurred on saponification of the β-keto ester.
(f) Product was an aromatic derivative (phenol).

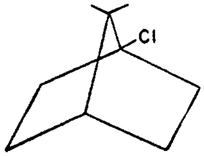
The structure of ethylene has been described (53, 72d, 117) as a planar arrangement with three orbitals (s, p_x, and p_y) of each carbon atom lying in a plane and hybridized to form three sp^2 bond orbitals with their bond directions (σ-bonds) in the plane. The fourth orbital (p_z) of each carbon atom has a node in the plane and lobes extending above and below the plane, and the two p_z orbitals of the adjacent carbon atoms, having electrons with opposite spins, overlap laterally to form what amounts to the second bond (π-bond) of the double bond. The maximum overlapping of the p_z orbitals occurs when they are parallel, i.e., when all six of the atoms are coplanar, and this interaction restricts rotation about the carbon–carbon axis. Prelog, Barman, and Zimmermann (124) considered that if a bridgehead double bond did occur in a small atomic-bridged-ring system the bridgehead carbon atom would deviate greatly from the planar trigonal σ-electron arrangement which is preferred in an ordinary double bond. Since the form and spatial arrangement of the p_z orbital can be altered to only a limited extent, such a steric situation would lead to an uncoupling of the π-electron system of the double bond and therefore to an increase in the energy level, that is, to a decrease in stability. Their view was that the facts which are described by Bredt's rule constitute examples of the steric hindrance of the resonance of the two π-electrons of a double bond and thus belong to the simplest case of steric hindrance of resonance electrons which is often found with conjugated systems. It seems likely that if unsaturation should occur at a bridgehead position in a relatively small bridged-ring system a normal double bond would not exist, but that diradical and/or dipolar forms would contribute greatly to the state of the molecule (69).

Bredt's rule has been used primarily with carbocyclic compounds where, in general, the saturated atoms have a tetrahedral configuration and two doubly bound atoms and their four substituents are coplanar. Wittig (197b) considered that the rule should also be applicable to nitrogen compounds, since this atom when tetravalent has a tetrahedral configuration similar to that of carbon, and the observations with a number of nitrogen-containing structures seem to justify this extension of the rule (*cf.* page 258). Doering and Levy (59) suggested that the rule may not apply to a carbon–sulfur double bond where there is the possibility of octahedral bond angles, but this question was not answered by the available data (*cf.* page 255).

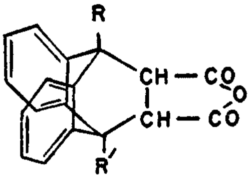
VI. APPLICATIONS OF BREDT'S RULE

A. DEHYDROHALOGENATION REACTIONS

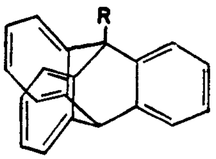
1. *Bicyclic compounds having halogen at the bridgehead position*



XVII
1-Chloroapocamphane



XVIII: R = Br, R′ = H
XVIIIa: R = R′ = Cl
XVIIIb: R = R′ = C_6H_5



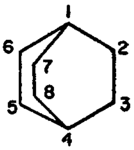
XIXa: R = Br
XIXb: R = H

(a) 1-Chloroapocamphane, 9-bromo- and 9,10-dichloro-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride, and 1-bromotriptycene

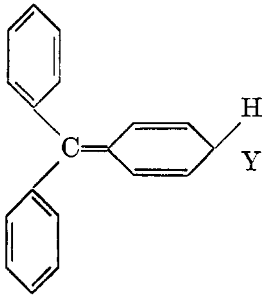
Bartlett and coworkers (19, 20, 21, 23) studied several bicyclic bridged-ring compounds having a bromine or chlorine substituent at the bridgehead position and found these halides to be extremely inert. When 1-chloroapocamphane (XVII) was heated for 21 hr. with 30 per cent potassium hydroxide in 80 per cent ethanol, it was recovered unchanged (20). When it was heated at the boiling point with silver nitrate in water–ethanol solution for 48 hr., conditions which might be expected to cause reaction *via* a carbonium-ion intermediate (72b), the solution remained clear with no opalescence and the starting material was again recovered. (Compare the reported replacement of OH by Cl in [3.3.1] system, page 236.) The similarly substituted halides diethyl *tert*-butylcarbinyl chloride and bornyl chloride in contrast were found to be quite reactive. The dibenzobicyclo͏öctane derivative XVIII, previously found by Barnett, Goodway, Higgins, and Lawrence (17) to be stable toward dehydrohalogenation, showed no replacement of the halogen on boiling for 18 hr. with 21 per cent potassium hydroxide (19). Similarly, 1-bromotriptycene (XIXa), in sharp contrast to triphenylmethyl halides, formed a colorless nonconducting solution in liquid sulfur dioxide. The bromine was unreactive when XIXa was heated in toluene solution with stannic chloride under conditions which produced chloroanthracene from anthracene dibromide. Bartlett and Lewis (21) considered these experiments to demonstrate that the positive triptycyl ion, if it exists at all, cannot be formed by methods applicable to analogous triarylmethyl compounds. No reaction was observed when 1-bromotriptycene was treated with copper powder, with zinc dust, or with molecular silver, the latter even at 280°C. in mineral oil. Reaction occurred slowly with sodium or with magnesium to form triptycene (XIXb), but attempts to isolate intermediate organometallic derivatives or carbonation products were not successful. It was concluded that if a free-radical intermediate occurs in this reaction, this triptycyl free radical must be more reactive toward hydrogen in the hydrocarbon solvent than ordinary aliphatic free radicals, thus differing markedly in stability from analogous triarylmethyl free radicals, in which resonance stabilization (118) can occur (see formula XXI). The low reactivity of these atomic-bridged-ring derivatives and the instability of the triptycyl free radical were accounted for by the steric limitations imposed by the ring system upon the bridgehead carbon atom (*cf.* "active" hydrogen in triptycene and the triptycyl carbanion, page 254).

Bartlett and Knox (20) explained the fact that dehydrohalogenation of 1-chloroapocamphane (XVII) did not occur by applying Bredt's rule to the cycloölefin which should be formed, and the circumstances with XVIII are comparable. They estimated that the bridgehead olefin bicyclo[2.2.2]-1-octene is more strained than the -2-octene isomer by approximately 22.5 kcal. per mole, indicating that here Bredt's rule is well justified thermodynamically. Rearrangement of the system into one capable of olefin formation, with accompanying inversion of carbon atom 1, is subject to the same kind of steric limitations as direct displacement (18, 22).

Some reactions of alkyl halides—for example, reaction of arylated methyl halides or of tertiary alkyl halides with silver nitrate—are considered to occur with the formation of intermediate solvated carbonium ions (72b, 166). A large amount of evidence indicates that these carbonium ions must be essentially planar. Bartlett and Knox (20) estimated that a strain of approximately 22.5 kcal. per mole would be required to force carbon atom 1 into the plane of atoms 2, 6, and 7 in the bicyclo[2.2.2]octane system (XX), and an even greater amount would be necessary in the apocamphane ring; hence ionization of these halides is greatly hindered. In compounds such as triphenylmethyl bromide ionization is facilitated, since the carbonium-ion intermediate is stabilized by the contribution of several resonance forms (XXI) which, ideally, require coplanarity of the rings and the central carbon atom. With the ion from the bridgehead halides, analogous structures would require a bridgehead double bond, and Bartlett and Cohen (19) considered that according to Bredt's rule they cannot contribute significantly to the resonance. In view of Swain's (166) recent work on the importance of the solvation of ionic reaction intermediates, Bartlett and Lewis (21) regarded it as an open question whether these resonance effects or the lack of solvation due to shielding by the bridged-ring system is the more important factor in the unreactivity of these halides. One may consider that hyperconjugative resonance structures such as XXII generally contribute to the stability of a tertiary carbonium ion, but if the central atom is a bridgehead, as in XVII, the occurrence of analogous forms also would be hindered.

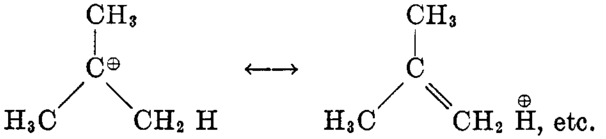


XX



XXI

(Y = $\oplus$, •, $\underset{..}{\ominus}$)



XXII

Clar (2, 47) attempted to dehydrohalogenate XVIIIa, obtained by the Diels–Alder condensation of 9,10-dichloroanthracene and maleic anhydride, by heating it with quinoline. He considered that the removal of 2 moles of hydrogen chloride should give a substance which would be formed in disagreement with Bredt's rule or which would be a free diradical. The product obtained, however, was 9,10-dichloroanthracene, the thermal reversal of the Diels–Alder condensation taking place in preference to the dehydrohalogenation. Clar (2, 47, 169) further observed that XVIIIa easily reacted with benzene in the presence of aluminum chloride, while the halogens in 9,10-dichloroanthracene were found to be inert in Friedel–Crafts syntheses. The product obtained was 9,10-diphenylanthracene and thus cleavage of the bridge, which took place on heating XVIIIa alone, occurred here also. It was considered that the reaction of 9,10-dichloroanthracene with maleic anhydride to form XVIIIa deprives the carbon atoms in the 9- and 10-positions of their aromatic character, thus increasing the reactivity of the chlorine atoms and making them replaceable, and XVIIIb was postulated as an intermediate in the Friedel–Crafts conversion of XVIIIa to 9,10-diphenylanthracene. In view of the work described above and the fact that the bridged-ring system is not preserved, it seems unlikely that it is in the original atomic-bridged-ring system XVIIIa that the halogens are reactive.

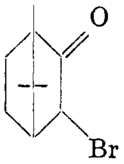
(b) α-Halocamphoric acid anhydrides

The earliest mention of what is now known as Bredt's rule was made by Bredt, Houben, and Levy (39) in a discussion of the dehydrohalogenation of α-halocamphoric acid derivatives (*cf.* page 220).

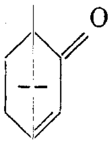
2. Bicyclic compounds having halogen adjacent to the bridgehead position

(a) 3-Bromocamphor

Schiff (142; see also 55) found that 3-bromocamphor (XXIII) on treatment with alcoholic potassium hydroxide unexpectedly gave camphor, and presumably potassium hypobromite. It was found (12) also that 3-bromocamphor could be heated with aniline or with quinoline without removal of hydrogen bromide, except for a small amount attributed to resinification, the bulk of the bromocamphor being recovered. This behavior could not be accounted for adequately by simple analogy with open-chain compounds, and in attempting to do so Aschan (12) doubted Bredt's structure for camphor on which that shown for the bromide is based.



XXIII
3-Bromocamphor



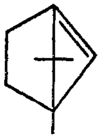
XXIV

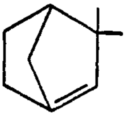
Bredt (44) explained these observations by calling attention to the fact that XXIII cannot split out hydrogen bromide to form the unsaturated ketone XXIV because here the double bond would lie at a bridgehead.[2]

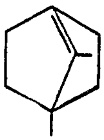
[2] Apparently the Favorskii rearrangement of the α-bromoketone XXIII also is hindered. Extensive decomposition occurred, possibly preceded by elimination reactions, rather than ring contraction to the expected strained cyclobutane derivative, in the attempted Favorskii rearrangement of 2-chlorocyclopentanone (64). Compare the pinacol rearrangement of *trans*-1,2-dimethyl-1,2-cyclopentanediol (18, 105).

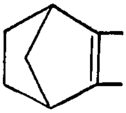
(b) "Camphenilyl chloride"; structure of "camphenilene"

An unsaturated hydrocarbon C_9H_{14}, designated "camphenilene,"[3] has been reported in several investigations to be obtained from camphenilol (XXXII) (*a*) by conversion to "camphenilyl chloride" (regarded as having structure XXXIII) with phosphorus pentachloride followed by dehydrochlorination with amines or sodium alkoxides and (*b*) by dehydration with potassium bisulfate. Several structures, including XXVI, XXVII, and XXVIII, which have been proposed (74, 79, 150, 158) for "camphenilene" are inconsistent with Bredt's rule.

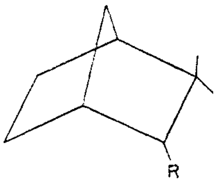

XXVI


XXVIII

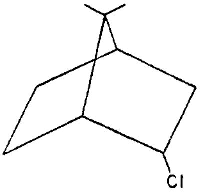

XXVII


XXIX
Santene

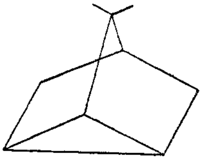
On the basis of this rule Meerwein (104a) criticized structure XXVIII, which Hintikka and Komppa (74) had proposed for the product obtained by route (*a*), and his suggestion that the material which they actually obtained was santene (XXIX) was confirmed by Komppa and Hintikka's (89, 90) reinvestigation, using routes (*a*) and (*b*). A mixture usually has been obtained and apobornylene (7,7-dimethylbicyclo[2.2.1]-2-heptene) and apocyclene (XXX) have been reported as other components. Structure XXVIII was revived by Snitter (158; *cf.* also 85) from an investigation of the Raman spectra of the materials obtained by routes (*a*) and (*b*), and it was again criticized according to Bredt's rule by Gratton and Simonsen (68), by Komppa and Nyman (91), and by Lipp and Daniels (98). The "camphenilyl chloride" was considered (81a, 91, 98) to be a mixture containing an apobornyl chloride (α-fenchocamphoryl chloride) (XXXI), and the problem is further complicated because the investigators used different reagents in the dehydrohalogenation reaction. Although it has been suggested



XXXII: R = OH
XXXIII: R = Cl



XXXI
α-Fenchocamphoryl chloride


XXX
Apocyclene

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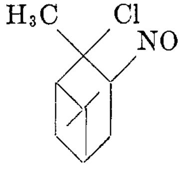
[3] The name "camphenilene" has also been used for 5,5-dimethylbicyclo[2.2.1]-2-heptene obtained, for example, by the dehydration of 5,5-dimethylbicyclo[2.2.1]-2-heptanol *via* the methyl xanthate ester (112).

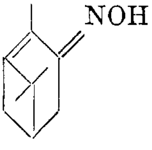
(155d) that a small amount of "camphenilene" (structure XXVIII) might actually be present, since ozonolysis apparently gave a small amount of an unidentified ketoaldehyde, there seems to be no satisfactory evidence to support structure XXVIII as an exception to Bredt's rule.

(c) α-Pinenenitrosochloride; structure of nitrosopinene and its derivatives

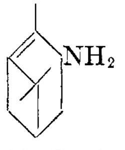
α-Pinenenitrosochloride, XXXIV (or dimeric structure), when treated with basic reagents such as alcoholic potassium hydroxide, loses hydrogen chloride to form a product, $C_{10}H_{15}NO$, designated nitrosopinene (171). Of the various structures proposed for nitrosopinene XXXV seems to have been accepted (141, 178, 180, 181) along with structure XXXVI for pinylamine, which is obtained from nitrosopinene by reduction with sodium and ethanol or with zinc and acetic acid. Ruzicka and Trebler (141) criticized these structures on the basis of Bredt's rule; their reinvestigation showed nitrosopinene to have structure XXXVII and pinylamine the corresponding structure XXXVIII, thus being derivatives of β-pinene. Pinocarvone oxime, usually regarded as having structure XXXVII, was considered by Ruzicka and Trebler to be stereoisomeric with nitrosopinene, but in more recent work Schmidt has concluded that the substance previously described as pinocarvone oxime is actually the oxime of myrtenal (*cf.* under carvopinone, page 262).



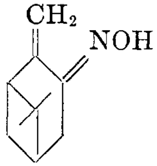
XXXIV
α-Pinenenitrosochloride



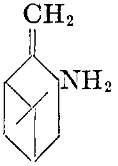
XXXV



XXXVI



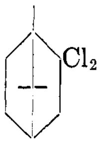
XXXVII
Nitrosopinene



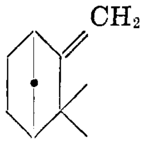
XXXVIII
Pinylamine

(d) α-Camphor dichloride and camphenilone dichloride

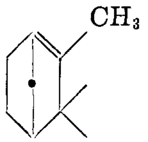
When dehalogenated by means of sodium, α-camphor dichloride (XXXIX) was reported (83) to form XL, and the product obtained similarly from camphenilone dichloride (XLI) was found (74) to be XLII. Meerwein (104b) pointed out that in these reactions the two probable primary hydrocarbon products XLIII and XLIV, respectively, are unstable and have a tendency to change over to a more stable form by displacement of the double bond. It seems probable



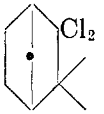
XXXIX
α-Camphor dichloride



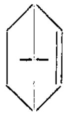
XL



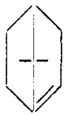
XLIII



XLI



XLII

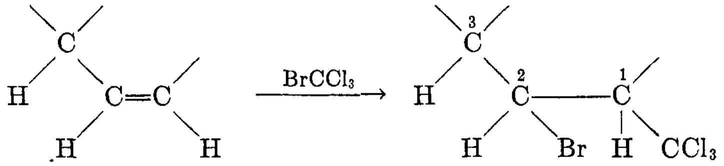


XLIV

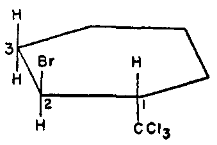
that XLIII and XLIV are never actually formed but that in each reaction the product-determining step is the removal of a hydrogen from a reaction intermediate with the formation of the double bond and that the loss of the hydrogen is favored in that direction which will give the olefin having the least strain.

(e) 2-Bromo-3-trichloromethylbicyclo[2.2.1]heptane, 2-bromo-3-trichloromethylbicyclo[2.2.2]octane, and 6(or 5)-bromo-5(or 6)-trichloromethyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoindene

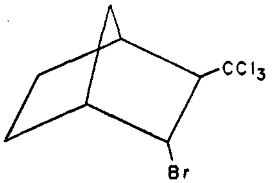
In studying the reactivity of olefinic double bonds in free-radical addition reactions Kharasch and Friedlander (84) obtained products of the type of XLV from various olefins and bromotrichloromethane. Adducts were obtained with open-chain, monocyclic, and bicyclic atomic-bridged-ring olefins and these three classes of addition products showed different behavior toward the dehydrohalogenating reagent alcoholic potassium hydroxide. With the open-chain compound derived from 1-octene the bromine was removed with a hydrogen from C_1 to form a trichloromonoene; with the monocyclic adduct derived from cyclohexene the bromine was removed with a hydrogen from C_3 and also a chlorine



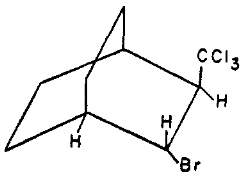
XLV



XLVIII



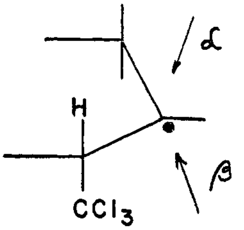
XLVI



XLVII

was removed with hydrogen from C_1 to form a dichloro conjugated diene; the bridged-ring derivatives, however, were quite resistant to the loss of hydrogen halide. XLVI did not react when heated at 50°C. with 0.7 *N* potassium hydroxide in absolute ethanol for 6 hr. Kharasch and Friedlander explained this stability of the bicyclic compounds XLVI, XLVII, and the dicyclopentadiene addition product by the use of Bredt's rule, since elimination of the bromine with hydrogen from C_3, as occurs with the monocyclic compounds, would require a double bond at a bridgehead, and the elimination with hydrogen from C_1 would not occur readily in view of the behavior of the monocyclic adducts described above.

The observed direction of elimination with the monocyclic adducts and the stability of the bicyclic derivatives suggest that *trans* addition of the bromine and trichloromethyl groups occurs as shown in XLVII and XLVIII, for then the hydrogen atom on C_1 would not be in the proper position for the preferred process of *trans* elimination of hydrogen bromide (54). It seems probable that the bromotrichloromethane molecule would approach the radical intermediate XLVIIIa from the direction α, rather than β, in order to remain farther removed from the $—CCl_3$ group (72a).



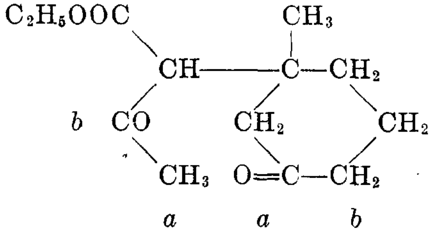
XLVIIIa

B. DEHYDRATION REACTIONS

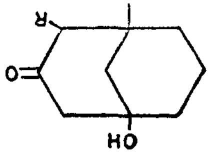
1. *Bicyclic compounds having hydroxyl at the bridgehead position*

(a) Substituted bicyclo[3.3.1]-1-nonanol-3-ones

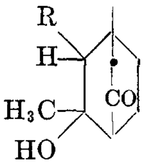
Rabe (132) investigated the cyclization of the diketo ester XLIXa and obtained (after hydrolysis of the ester group) a bicyclic β-hydroxyketone which was remarkably stable toward dehydration (*cf.* page 221). He considered that, depending on the manner in which the ring closure occurred, either a bicyclo[3.3.1]nonane derivative XLIXb (ring closure through groups *a—a*) or a bicyclo[2.2.2]octane derivative XLIXc (ring closure through groups *b—b*) would be formed. Rabe favored the bicyclononane structure (XLIXb) on the basis of strain considerations, assuming a planar cyclohexane ring in XLIXa. Ruzicka (137) called attention to the fact that, according to Bredt's rule, dehydration of a compound having structure XLIXb should not occur readily because this would form a double bond at the bridgehead. After the introduction of the concept of a strainless nonplanar cyclohexane ring, Mohr (110) pointed out that formation of either structure XLIXb or XLIXc should be possible without steric difficulties and that XLIXb was not necessarily favored, as Rabe had assumed. He suggested that further experimental proof was needed. In later work Rabe and Appuhn (131) obtained additional data to support the bicyclononane structure XLIXb. They felt that although, according to Bredt's rule, either structure accounted for the resistance of the β-hydroxyketone to the facile dehydration which is typical of nonbridged β-hydroxyketones, the stability of the monocarbinol obtained on reduction of the carbonyl group was best explained by assuming structure XLIXb. The carbinol (XLIXd) resisted dehydration on heating with zinc dust at 230°C. or on heating the xanthate ester, and the chloride (XLIXe) obtained from the carbinol and phosphorus pentachloride failed to eliminate hydrogen chloride when heated at the boiling point (193°C.) with dimethylaniline. Rabe and Appuhn considered the stability of these compounds according to Bredt's rule as convincing evidence in favor of the bicyclononane structure XLIXb, which would lead to the indicated derivatives with the hydroxyl and chlorine groups at the bridgehead position. If the carbinol were derived from XLIXc it could presumably undergo dehydration by loss of a nonbridgehead hydrogen.



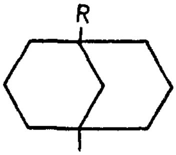
XLIXa



XLIXb



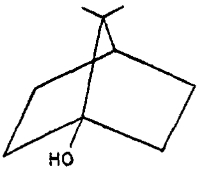
XLIXc



XLIXd: R = OH
XLIXe: R = Cl

(b) 1-Apocamphanol

Bartlett and Knox (20) found that 1-apocamphanol (L), in spite of being a tertiary alcohol, dissolved reversibly with no evidence of reaction in concen-



L

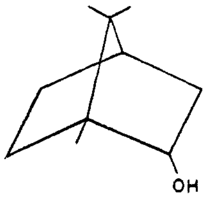
1-Apocamphanol

trated sulfuric acid. This suggested to them that dehydration and molecular rearrangement leading to dehydration are prohibited in this compound, as one should expect from Bredt's rule and other considerations (20) concerning rearrangement (*cf.* 1-chloroapocamphane, page 228).

2. Bicyclic compounds having hydroxyl adjacent to the bridgehead position

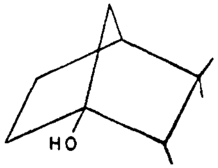
(a) "Isoborneol" and camphenilic acid

Shortly after Bredt first discussed the problem of dehydrocamphoric acid anhydride Moycho and Zienkowsky (111) described their work with isoborneol (LI) and camphenilic acid (LII). Under the assumption that the structure of isoborneol was LIII, they pointed out that in these two structures simple dehydration would lead to a double bond at a bridgehead in disagreement with Bredt's rule. One product from the dehydration of isoborneol is cyclene, and from the assumed structure for the former and Bredt's rule they suggested that LIV could be the structure of cyclene, the dehydration occurring so as to form a new three-membered ring. Since the structures of isoborneol (LI) (81c) and cyclene (LV) are now considered to be different from those assumed by Moycho and Zienkowsky, this application of Bredt's rule is of limited interest. Dehydration for such a structure (LIII) as they assumed for isoborneol should be similar to that for 1-apocamphanol (L), discussed by Bartlett and Knox (20). From camphenilic acid (LII) the products were reported to be dehydrocamphenilic acid (tricyclenic acid; LVI) (*cf.* page 261) and an unsaturated hydrocarbon "camphenilene" (santene (XXIX)), the reaction apparently being similar to the dehydration of the structurally similar camphenilol (page 232).

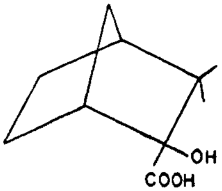


LI

Isoborneol

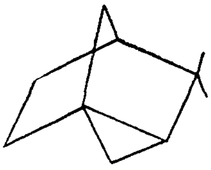


LIII

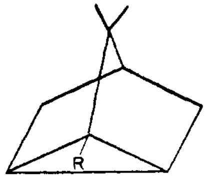


LII

Camphenilic acid



LIV



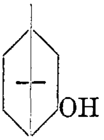
LV: R = CH_3
LVI: R = COOH

(b) Camphenilol

See the dehydrohalogenation of "camphenilyl chloride" (page 232).

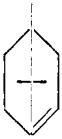
(c) Epiborneol

The dehydration of epiborneol (LVII) by heating the methyl xanthate ester was found by Bredt and Perkin, Jr., (40, 41) to give bornylene (LVIII). That LVIII is formed rather than the strained dehydrocamphane (LIX) was cited by Bredt (44) in support of the rule.



LVII
Epiborneol

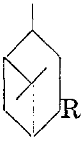
LVIII
Bornylene



LIX
Dehydrocamphane

(d) Verbanol

Dehydration of verbanol (LXV) by heating the methyl xanthate ester was reported by Wienhaus and Schumm (188) to give δ-pinene (LXII). The same product was obtained (187) by the Hofmann exhaustive methylation of verbanylamine *via* its quaternary ammonium hydroxide (LXVI). It was pointed out (168b) that these elimination reactions can go in only this one direction if the pinane ring system is to remain intact.

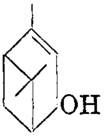


LXV: R = OH

LXVI: R = $\overset{\oplus}{N}(CH_3)_3\overset{\ominus}{OH}$

(e) Verbenol

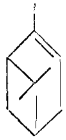
Blumann and Zeitschel (29, 30) reported the diene verbene, obtained by dehydration of verbenol (LX) with acetic anhydride, to have structure LXI. Reduction of verbene with sodium and alcohol forms dihydroverbene which they considered to be LXII, although the properties of the hydrocarbon and several of its derivatives were observed to be quite similar to the properties of α-pinene (LXIII) and its derivatives. Ruzicka and Trebler (138, 141) called attention to the fact that the proposed structure LXI is in conflict with Bredt's rule, and the alternative structure LXIV was suggested for verbene. It was concluded



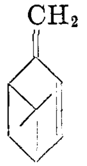
LX
Verbenol

LXI

LXII
δ-Pinene



LXIII
α-Pinene

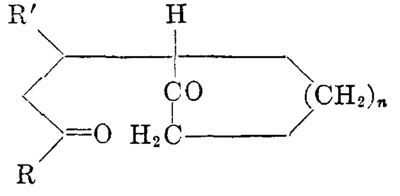


LXIV
Verbene

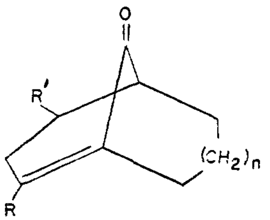
that the dihydroverbene obtained by reduction was actually α-pinene (LXIII). Structure LXIV for verbene was further supported by an investigation (60) of its Raman spectrum, and this structure (LXIV) has been recorded in later compilations (25a, 81b).

(f) Substituted 2-hydroxybicyclo[*n*.3.1]-ω-alkanones (n = 3–12)

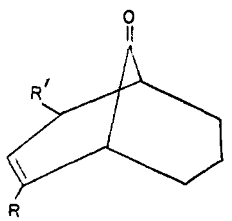
Stobbe and coworkers (67, 163, 164) prepared several unsaturated bicyclic ketones by the intramolecular aldol condensation of monocyclic 1,5-diketones of the type of LXVII, and they assumed the double bond formed on dehydration of the intermediate aldols to be at the bridgehead position as in LXVIII. The position of the double bond in LXVIIIa was questioned by Mohr (110), who referred to Bredt's rule. Allen and Sallans (6) repeated some of Stobbe's work and extended it to other analogs, including LXVIIIb (or LXIXa), in which they also assumed the bridgehead position for the double bond. In reviewing this work Allen (3e) pointed out that this location is contrary to Bredt's rule, but on the basis of the indirect evidence available at the time he concluded that these substances constitute exceptions to the rule. It was again pointed out (81d) that structures like LXVIII would be highly strained, if not altogether impossible. An investigation (50) of the ultraviolet absorption spectra of the diphenyl-substituted unsaturated ketone LXVIIIb (or LXIXa) and some related



LXVII: $n = 0, 1; R = R' = C_6H_5$

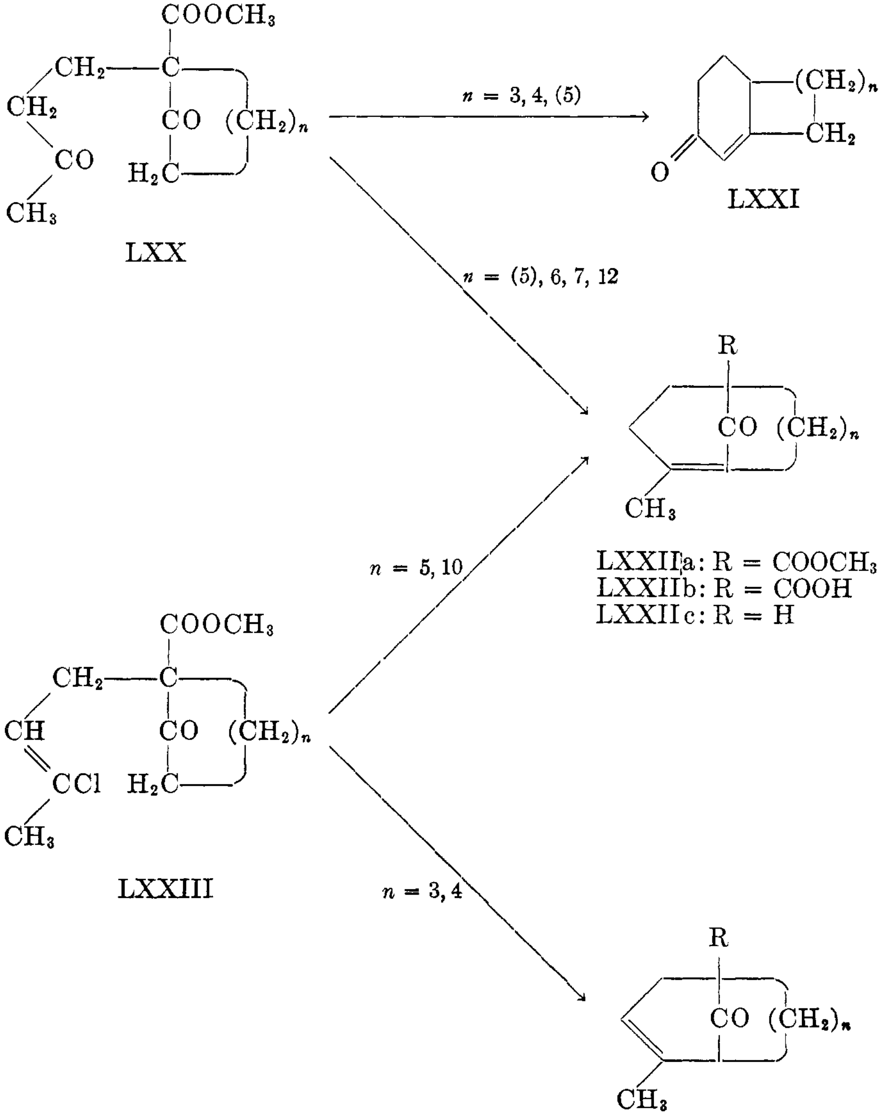


LXVIIIa: $n = 0; R = R' = C_6H_5$
LXVIIIb: $n = 1; R = R' = C_6H_5$
LXVIIIc: $n = 1; R = C_6H_5; R' = H$



LXIXa: $R = R' = C_6H_5$
LXIXb: $R = C_6H_5; R' = H$

compounds has provided evidence that the double bond is not in the α,β-(bridgehead) position. With the alternative structure LXIXa having a β,γ-double bond, therefore, this compound (and presumably the other small-ring ones prepared in the same way) does not appear to be an exception to Bredt's rule. The related monophenyl-substituted unsaturated ketone similarly was shown (51) by means of the ultraviolet absorption spectrum of its 2,4-dinitrophenylhydrazone to have a β,γ-(LXIXb) rather than an α,β-(bridgehead) double bond (LXVIIIc).



LXX

LXXI

LXXIIa: R = $COOCH_3$
LXXIIb: R = $COOH$
LXXIIc: R = H

LXXIII

LXXIVa: R = $COOCH_3$
LXXIVb: R = $COOH$
LXXIVc: R = H

Prelog and coworkers (123, 124, 127) studied the cyclization of a series of 2-carbomethoxy-2-(3-ketobutyl)cycloalkanones (LXX) and 2-carbomethoxy-2-(3-chlorocrotyl)cycloalkanones (LXXIII) in which the rings contained from six to fifteen carbon atoms. The products obtained were bicyclic unsaturated ketones or β-keto esters, as summarized in table 1. Cyclization of LXX through an intramolecular aldol condensation was accomplished by heating with acetic acid containing aqueous hydrochloric acid. Decarboxylation also occurred giving an α,β-unsaturated ketone, the skeleton structure of which depended upon the ring size of the starting material. With a small ring (LXX: $n = 3$ or 4) the valence-bridged-ring (fused-ring) bicyclo[$(n + 1).4.0$] structure LXXI was formed, but with a larger ring (LXX: $n = 6$, 7, or 12) the product was an atomic-bridged-ring bicyclo[$n.3.1$] derivative (LXXIIc). With a ring of intermediate size (LXX: $n = 5$) there was obtained a mixture of LXXI and LXXIIc. The double bond in LXXI and in LXXII was shown by means of ultraviolet absorption spectra to be in the bridgehead (conjugated) position.

TABLE 2

Bicyclic bridged-ring compounds obtained from nitromalonaldehyde and monocyclic ketones

(Prelog and Wiesner (128))

RING SYSTEM [n.3.1]		IMMEDIATE PRODUCT IN ALKALINE SOLUTION (SALT)	PRODUCT OBTAINED ON ACIDIFICATION
n	S*		
3	(7)	(No product isolated)	
4	(8)	(No product isolated)	
5	9	Colorless, LXXVb	LXXVd (keto form)
6	10	Colorless, LXXVb	LXXVe (phenol form)
7	11	Yellow, LXXVc	LXXVe (phenol form)
9–15	13–19	Yellow, LXXVc	LXXVe (phenol form)
17	21	Yellow, LXXVc	LXXVe (phenol form)
18	22	Yellow, LXXVc	LXXVe (phenol form)
27	31	Yellow, LXXVc	LXXVe (phenol form)

*$S = [n + 3 + 1]$.

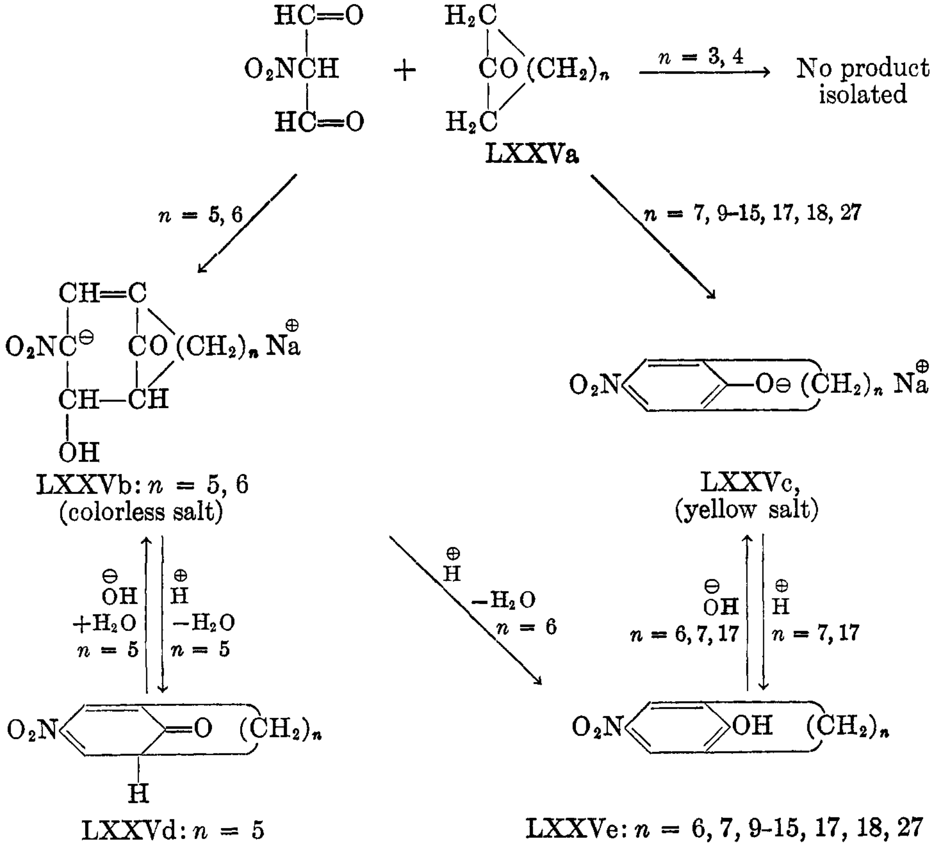
When LXXIII was cyclized with concentrated sulfuric acid decarboxylation did not occur and, regardless of the ring size, an atomic-bridged-ring bicyclo[$n.3.1$] unsaturated β-keto ester was obtained. The position of the double bond, however, depended on the ring size of LXXIII. With a small ring (LXXIII: $n = 3$ or 4) the product was LXXIVa with a nonconjugated double bond, while from a larger-ring structure (LXXIII: $n = 5$ or 10) there was obtained LXXIIa having conjugated (α,β-) unsaturation at the bridgehead. The position of the double bond in these products also was determined by study of their ultraviolet absorption spectra.

From this work it was concluded by Prelog and coworkers (123, 124, 127) that in considering stable isolable compounds Bredt's rule does not forbid a bridgehead double bond for the bicyclo[5.3.1]undecene ($S = 9$) system but that it probably does forbid a bridgehead double bond in the bicyclo[4.3.1]decene ($S = 8$) system and in bicyclo[3.3.1]nonene ($S = 7$) and its nitrogen analogs (*cf.* page

265). They provided an experimental verification of the viewpoint expressed earlier by Bredt (34) that with large rings the rule should not forbid a bridgehead double bond; furthermore, they determined the limiting ring size for the special case of a bridgehead double bond which is contained in the [3] branch of the bicyclo[n.3.1] system and which is also conjugated with a carbonyl group.

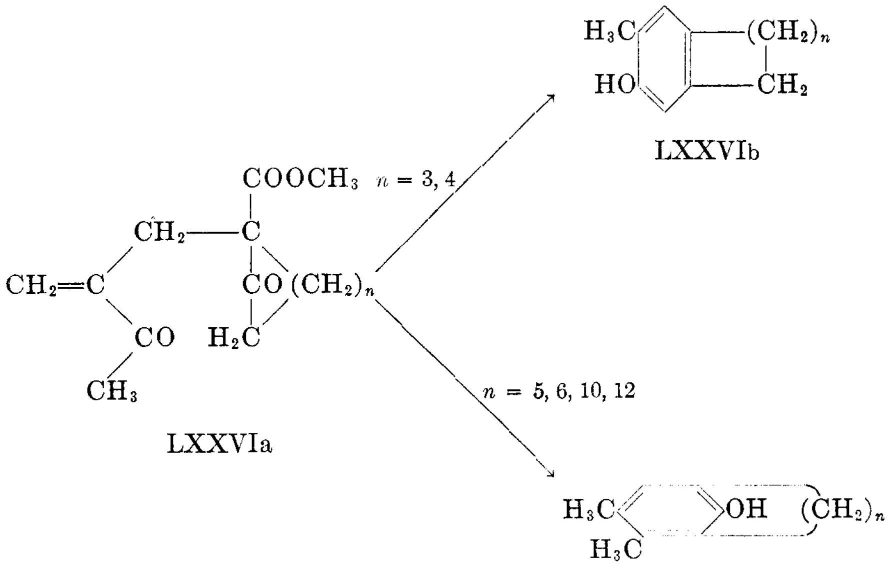
Prelog, Barman, and Zimmermann (123, 124) discussed the theoretical significance of a strained bridgehead double bond (page 227), and the decarboxylation of the bicyclic β-keto acids derived from some of these compounds was also described (*cf.* page 246).

Prelog and Wiesner (123, 128) investigated the formation of meta-bridged *p*-nitrophenol derivatives or related compounds by the condensation of nitromalonaldehyde with monocyclic ketones in the presence of sodium hydroxide, a method which presumably involves aldol intermediates having hydroxyl adjacent to the bridgehead. The type of product formed was found to depend upon the ring size of the ketone used. With the smaller-ring ketone (LXXVa: n = 3 or 4) no product was isolated. Using a larger ring (LXXVa: n = 7, 9–15, 17, 18, 27) the yellow *p*-nitrophenoxide salt (LXXVc) was formed directly and on acidification the meta-bridged *p*-nitrophenol LXXVe was obtained, corresponding to the behavior with open-chain analogs of LXXVa (*cf.* table 2).



With a ring of intermediate size (LXXVa: $n = 5$ or 6), however, only one molecule of water was eliminated in the alkaline condensation reaction and the immediate product was a colorless salt for which structure LXXVb was considered probable. Dehydration occurred on acidification of the colorless salt (LXXVb) giving with $n = 6$ the *p*-nitrophenol LXXVe, but with $n = 5$ the nonaromatic keto form LXXVd. The isolation of a compound with structure LXXVd ($n = 5$) further supports the statement of Bredt's rule to permit a bridgehead double bond in the [5] or the [3] branch of the bicyclo[5.3.1]undecene ($S = 9$) system. Evidently the coplanarity requirements for the formation of the second bridgehead double bond in the [1] branch in LXXVd → LXXVe ($n = 5$, $S = 9$) would cause such a total strain that the ketone does not enolize even though this process would aromatize the ring.

The aromatic phenol form of this same ring size ($S = 9$) was obtained, however, in a dimethyl series starting with the condensation of monocyclic β-keto



LXXVIa

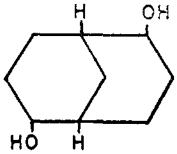
LXXVIb

LXXVIc

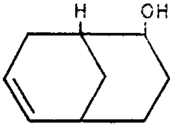
esters with the quaternary base of 1,1-bis(diethylaminomethyl)acetone. Using a large-ring β-keto ester Prelog, Wirth, and Ruzicka (130) obtained LXXVIa ($n = 10$), which on heating with acetic and hydrochloric acids gave the meta-bridged phenol LXXVIc ($n = 10$). Prelog, Barman, and Zimmermann (125) extended this work and found that from the condensation products LXXVIa, with $n = 3$ or 4, a fused-ring phenol (LXXVIb) was formed, but with LXXVIa ($n = 5$, 6, or 12) the product was the meta-bridged-ring derivative LXXVIc, as obtained in the earlier work. Thus the smallest meta-bridged benzene derivative in this series contained five members ($S = 9$), while with the 4-nitrophenols it was six members ($S = 10$). It was suggested (125) that the nonaromatic nitro derivative LXXVd is better stabilized by resonance than the analogous dimethyl compound would be, and that accordingly the increase in stability to be gained by aromatization is not as great in the nitro series as with the dimethyl compounds. The strain associated with the ring size $S = 9$ thus hinders aromatization of the nitro compound LXXVd but not of the dimethyl compound.

Evidence for the structures of these products was obtained from a study of their ultraviolet absorption spectra and their acidities. The *p*-nitrophenol derivatives were further converted to the aminophenols, to the hydroquinones, and to the quinones with meta "bridges," and the properties of these materials were also investigated (123, 128).

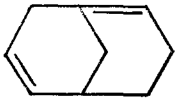
A number of investigators (e.g., 77a) have described meta- and para-bridged benzene ring compounds having large "bridges" which are presumably strainless and do not violate Bredt's rule. There apparently have been no experimental reports of the ring size required for two bridgehead double bonds which are not part of an aromatic ring (*cf.* page 226).



LXXVIIa



LXXVIIb



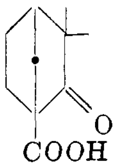
LXXVIIc

(g) Bicyclo[3.3.1]-2,6-nonanediol and bicyclo[3.3.1]-6-nonen-2-ol

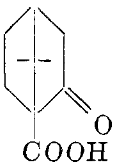
It was found (106) that one molecule of water could be eliminated from the diol LXXVIIa to form an unsaturated alcohol considered to have a nonbridgehead double bond (LXXVIIb), but attempts to prepare a diene by removal of the second molecule of water were unsuccessful. Similar results were obtained on deamination of the corresponding diamine. When attempted dehydration of LXXVIIb was forced, complete resinification occurred and no bicyclo[3.3.1]-2,6-nonadiene was isolated. It was considered (106) probable that in the forced removal of the second molecule of water the steric arrangement was such as to lead not to the -2,6-diene but to the -2,5-diene (LXXVIIc) and that this intermediate, being unstable as would be expected from Bredt's rule, underwent bridge cleavage to a readily polymerized methylcycloöctatriene. Bredt at one time (34) suggested that there was a preference for the hydroxyl groups in LXXVIIa to be eliminated with the tertiary (bridgehead) hydrogens and that the first dehydration actually forms a bridgehead double bond, resulting in a moderate amount of strain. He considered this strain to be transmitted in part to the other ring, and as a consequence the second dehydration to form an additional bridgehead double bond would introduce a prohibitive amount of strain, i.e., the second elimination was hindered according to Bredt's rule. In this connection Bredt cited the observed decarboxylation of the [3.3.1] β-keto acids (page 246) as evidence for the possible existence of a bridgehead double bond in the [3.3.1] system. Bredt here evidently failed to distinguish between the steric requirements for the existence of isolable compounds and transient reaction intermediates. While there are known cases of decarboxylation of β-keto acids having the β-keto group in a [3] branch of the [3.3.1] system, thus indicating the possibility of a transient intermediate with a bridgehead double bond, a number of instances are known in which dehydrations in the [3.3.1] structure avoid the formation of an isolable product having a bridgehead double bond on the [3] branch (*cf.* page 239).

C. DECARBOXYLATION OF β-KETO ACIDS HAVING A BRIDGEHEAD CARBOXYL GROUP

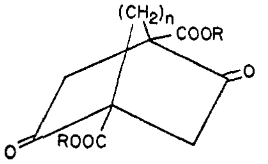
Although open-chain and monocyclic β-keto acids generally undergo decarboxylation readily, a number of bridged-ring compounds having the carboxyl group at the bridgehead position have been observed to be quite resistant to loss of carbon dioxide. It was reported by Aschan (13) that camphenonic acid (LXXVIIIa) distilled without decomposition at 310–312°C. under atmospheric pressure. Ketopinic acid (LXXVIIIb) was found (13, 88, 182) to be similarly stable toward decarboxylation, and conditions sufficiently drastic to cause loss of carbon dioxide also caused ring cleavage. Guha (70, 71) described the bicyclic diketo diacid LXXIXa as being resistant to the loss of carbon dioxide when its ester LXXIXb was heated at 200°C. for 30 min. in an autoclave with dilute hydrochloric acid, or when subjected to other similar acidic conditions. Removal of one carboxyl group to give a low yield of LXXX, however, was reported to occur when the acid LXXIXa was heated at 270–280°C. under reduced pressure (*cf.* page 248). Guha also prepared the ester LXXIXc and this compound likewise resisted decarboxylation. The bicyclo[3.3.1]nonane derivative LXXXIa (49), prepared by intramolecular aldol condensation (*cf.* page 239), was not decarboxylated on heating in a solution of acetic acid and aqueous hydrochloric acid, nor on sublimation at 150°C. under reduced pressure. Similarly, LXXXIb (52) was not decarboxylated on heating alone or in the presence of quinoline or copper, and the corresponding saturated compound was also stable (52). The



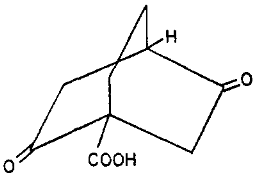
LXXVIIIa
Camphenonic acid



LXXVIIIb
Ketopinic acid

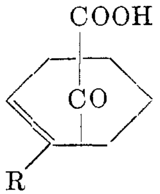


LXXIXa: $n = 2, R = H$
LXXIXb: $n = 2, R = C_2H_5$
LXXIXc: $n = 3, R = C_2H_5$



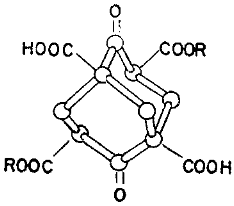
LXXX

[3.3.1] β-keto acid LXXIVb ($n = 3$; page 240) obtained by Prelog and coworkers (123, 124, 127) resisted the elimination of carbon dioxide. While the [n.3.1] derivative LXXIVb ($n = 3$) was unaffected by heating with quinoline at 240°C., the higher homolog ($n = 4$) and LXXIIb ($n = 5$) (from LXXIII) readily lost carbon dioxide under these conditions. With a still larger ring (LXXII: $n = 10$) the free acid was not isolated, since decarboxylation occurred even during alkaline hydrolysis of the ester (LXXIIa: $n = 10$) (table 1). Decarboxylation of bicyclo[n.3.1] derivatives (LXXII: $n = 5$, 6, 7, and 12) occurred during the formation of the bicyclic system from LXX (table 1).

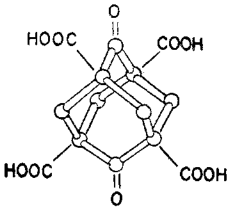


LXXXIa: R = C_6H_5
LXXXIb: R = H

In contrast to the stability of the [3.3.1] acids described above, Meerwein (106) found that LXXXIIa lost all four carboxyl groups (*cf.* page 248), two of which are at bridgeheads, when heated with water in an autoclave at 220°C. for 1 hr. Similarly, LXXXIIb lost 2 moles of carbon dioxide from the free carboxyl groups at the bridgeheads. The tricyclic structure LXXXIII formed from LXXXII by introduction of an additional methylene bridge, however, was reported by Böttger (32) to be extremely resistant to decarboxylation.

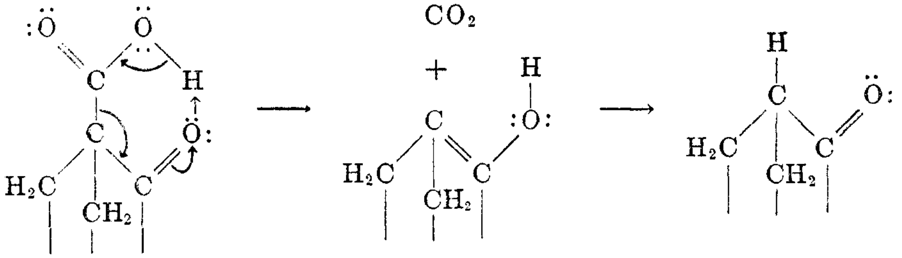


LXXXIIa: R = H
LXXXIIb: R = CH_3



LXXXIII

In the decarboxylation of β-keto acids Bredt (34) suggested that the hydrogen of the carboxyl group migrates to the keto oxygen and simultaneously carbon dioxide splits out, producing the enol form of the product, which subsequently ketonizes. The stability of LXXVIIIa, LXXVIIIb, LXXIXa, and LXXXIII was interpreted by him as being due to the steric difficulty, according to the rule, of obtaining the enol form of the expected products. The work of several investigators (121, 122, 183) has shown that α,α-disubstituted β-keto acids undergo decarboxylation, that the decomposing acid absorbs 1 mole of bromine at the same rate as carbon dioxide is evolved, and that the rate of decarboxylation is essentially independent of the dielectric constant of the solvent used. These observations have been interpreted to mean that the keto form of the keto acid can undergo the reaction, enolization of the keto acid before decarboxylation not being a prerequisite, and that the immediate product is the enol form of the ketone formed *via* a cyclic intermediate. The mechanism of the thermal decarboxylation of β-keto acids has accordingly been written (10) as follows with a quasi-ring intermediate, which is essentially Bredt's picture of the reaction in modern terms. When the α-carbon is a bridgehead in a small atomic-bridged-ring system one might expect on the basis of this mechanism and Bredt's rule that the decarboxylation will be hindered. The extent to which the reaction is hindered will, of course, be influenced by the factors which affect the strain associated with the corresponding bridgehead double bond, such as ring size and location of the β-keto group. Prelog (123) considered that the decarboxylation results can be related to Bredt's rule by assuming that in this reaction an anion at the bridgehead is an intermediate, which must be stabilized by resonance with the carbonyl group for the activation energy to be sufficiently low to permit the reaction.

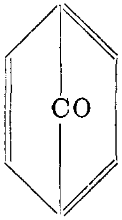


LXXXIV

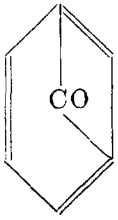
In the use of Bredt's rule there may arise the problem of how "stable" a structure must be to be considered in connection with the rule. It seems likely that a bridgehead double bond might occur in a transient intermediate and yet the corresponding or analogous structure with the double bond fixed at the bridgehead may be too unstable to be isolated under ordinary conditions. Bredt considered that in the isolable anhydride of tetrahydroisophthalic acid (CIII), which has the bicyclo[3.3.1] ring system, the double bond cannot be at the bridgehead and this conclusion is supported by later work with CIII (page 256) and by results with other [3.3.1] derivatives (*cf.* page 239), yet he suggested that LXXXII can have a bridgehead double bond as required by his picture of the decarboxylation reaction. These comments imply a distinction between isolable compounds and transient reaction intermediates, although Bredt did not make use of this contrast in his discussion of the dehydration of bicyclo[3.3.1]-6-nonen-2-ol (LXXVIIb, page 244). Similarly, Prelog and coworkers found the double bond in the isolable bicyclo[4.3.1]decene derivative LXXIVb to be in the β,γ- rather than the α,β-(bridgehead) position; yet this acid undergoes decarboxylation when heated with quinoline at 240°C. If the cyclic mechanism applies to this decarboxylation, the circumstances are analogous to the [3.3.1] systems above. Conclusions about the rule in the borderline area will thus depend in part on how one interprets the qualitative word "stable."

An additional example of the inherent qualitative nature of Bredt's rule is suggested by a comparison of the decarboxylation of the bicyclo[3.3.1]-β-keto acids ($S = 7$), in which it seems that the different positions of the double bond actually correspond to different stabilities. With acids LXXXI (page 246) the enol form of the expected products would have a 1,9-double bond in the [1] branch of the [3.3.1] system, while with LXXXIIa and LXXXIIb the double bond would be in the 1,2-position and thus in one of the [3] branches; the former did not undergo decarboxylation but the latter did. From a consideration of ball-and-peg models one would expect the 1,9-double bond in the [1] branch to result in appreciably more strain than the 1,2-double bond in a [3] branch (compare page 226). If one regards the transient intermediate implied by the cyclic mechanism LXXXIV (or the resonance-stabilized bridgehead anion) to have a bridgehead double bond sufficiently tangible to be pertinent to Bredt's rule, then in borderline cases the predictions from the rule may depend on which of the bridgehead positions the double bond occupies. With the present experimental data it does not seem profitable to try to define Bredt's rule in such detail, but to consider that the rule is inherently a qualitative one. Thus there are some examples of decarboxylation for the [3.3.1] system ($S = 7$), and on this basis Bredt's rule would apply to these transient intermediates only with values of S lower than 7. If the reported conversion of the [2.2.2] acid LXXIXa ($S = 6$) to LXXX (page 245) actually occurs *via* the enol form, the rule would apply only with values lower than $S = 6$, although such an enol structure with $S = 6$ would be expected to have an extremely short life. Further work is needed to determine the applicability of the rule in such areas.

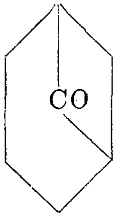
Zelinsky (204) attempted to prepare bicyclo[2.2.1]-7-heptanone by pyrolysis of *trans*-hexahydroterephthalic acid and its salts, but he evidently obtained little if any of the desired product (3b, 200). The ketones LXXXVa and LXXXVb, according to Stark (162), might be expected to be formed by pyrolysis of terephthalic and isophthalic acids, respectively. Stark (162) obtained a ketone by heating the calcium salt of *cis*-hexahydroisophthalic acid and assumed its structure to be LXXXVc, but Ruzicka and Trebler (140) pointed out that Stark's data are in better agreement with the properties of the unsaturated ketone 6-methyl-2-cyclohexenone (3b, 31, 110). Woodward, Brutschy, and Baer (200) commented that the conversion of dicarboxylic acids to ketones is often assumed to proceed through β-keto acid intermediates and that in the case described by Zelinsky such an intermediate would not be susceptible to decarboxylation. A β-keto acid intermediate from the hexahydroisophthalic acid similarly would be expected to resist decarboxylation.



LXXXVa



LXXXVb



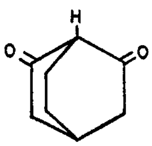
LXXXVc

The aromatic acids do not have α-hydrogens and the formation of a β-keto acid intermediate should not be expected for this reason as well as because of Bredt's rule, and any other route leading to LXXXVa or LXXXVb would be hindered according to the rule.

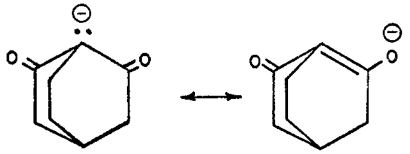
D. ENOLIZATION AND RELATED REACTIONS OF COMPOUNDS CONTAINING ACTIVE HYDROGEN

1. Bicyclo[2.2.2]-2,6-octadione

Bicyclo[2.2.2]-2,6-octadione (LXXXVIa) was prepared by Bartlett and Woods (24) as an example of a 1,3-diketone in which enolization involving the central hydrogen would constitute a violation of Bredt's rule. In contrast to analogous open-chain diketones LXXXVIa gave no color with ferric chloride, gave no copper salt, showed no greater solubility in aqueous alkali than in pure water, and in a Zerewitinoff determination consumed 2 moles of Grignard reagent and evolved only 0.15 mole of gas. Bartlett and Woods explained this non-enolic character in terms of the resonance in the negative ion remaining when the proton is removed: because the central carbon is a bridgehead, a double-bonded structure such as LXXXVIb, which would ordinarily stabilize the enolate anion of a 1,3-diketone, cannot contribute to the resonance.



LXXXVIa

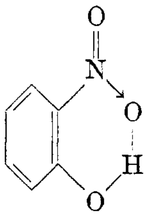


LXXXVIb

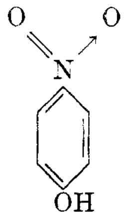
2. Monocyclic 1,3-diketones and substituted phenols

A number of differences are encountered in a comparison of the properties of certain isomeric substituted phenols, and also in a comparison of open-chain and monocyclic 1,3-diketones. These effects have been explained as being due to the steric arrangement of the groups, but Bredt's rule apparently has not been referred to in these discussions, although it provides a simple expression of the steric hindrance of chelation in many instances.

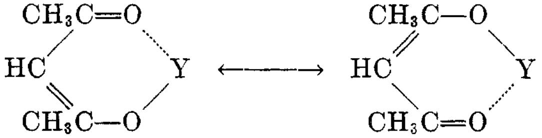
The volatility and solubility properties of some ortho-substituted phenols show characteristic differences from those of the meta and para isomers, and Sidgwick (153a) accounted for these results by considering chelation. He regarded the ortho derivative as existing in a chelate form (LXXXVIIa), where hydrogen bonding occurs intramolecularly. Sidgwick pointed out that analogous chelation cannot occur with the meta or para compounds, because an aromatic derivative cannot form a meta or para bridge (*cf.*, however, page 244), and thus with these isomers hydrogen bonding occurs intermolecularly, resulting in association. According to Bredt's rule chelate formation with LXXXVIIb to give a modified bicyclo[4.2.2] system with bridgehead double bonds would be hindered. There are of course other factors to be considered, such as the size of the chelate ring and the possibilities for resonance.



LXXXVIIa

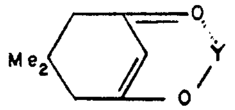


LXXXVIIb

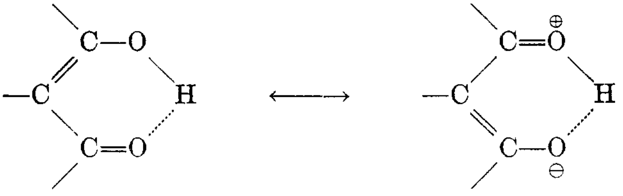


LXXXVIIIa: Y = H
LXXXVIIIb: Y = metal, e.g., Al, Be, Cu . . . (one equivalent)

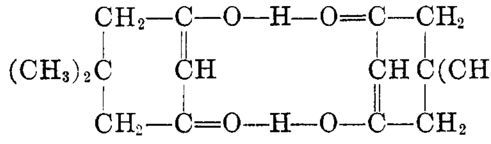
A number of properties of the enol form of an open-chain 1,3-diketone and its metal derivatives have been interpreted in terms of cyclic, resonance-stabilized chelate structures of the type of LXXXVIIIa and LXXXVIIIb. Monocyclic 1,3-diketones such as the dihydroresorcinol derivatives 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione (dimedon), on the other hand, have been found to differ from their open-chain counterparts in a number of instances where chelation might be expected. The contrast between the open-chain and cyclic diketones has been made in discussions of acidity (26, 148, 153b, 167, 186), of the effect of solvents on the keto–enol equilibrium (9), and of absorption spectra (28, 133), and it has been pointed out that, although enolization can occur, steric factors prevent chelation of the enol form of the cyclic 1,3-diketones. In studying the effect of structure on absorption spectra, Blout, Eager, and Silverman (28) examined dimedon and 2-ethyl-4-*n*-propyl-1,3-cyclopentanedione. These cyclic diketones showed a shift in the ultraviolet absorption maximum toward longer wave lengths on dilution, while no such change was observed with noncyclic 1,3-diketones, and this effect was attributed to ionization. They assumed that this phenomenon of increasing dissociation on dilution and the related shift in absorption spectrum is typical of all cyclic 1,3-diketones having at least one enolizable hydrogen on the carbon between the carbonyl groups. The fact that the spectrum of open-chain diketones did not depend on concentration was considered to be due to the occurrence of intramolecular hydrogen bonding, which is not possible with the cyclic derivatives because of the fixed spatial arrangement of the carbon–carbon bonds. Rasmussen, Tunnicliff, and Brattain (133) accounted for the spectra of enolized 1,3-diketones by the resonance-stabilized chelate form LXXXVIIId, referred to as "conjugated chelation" to differentiate it from ordinary intramolecular hydrogen bonding. They considered the spectrum of dimedon, which indicated this "conjugated chelation" type of enolization, to illustrate a type of structure in which resonance stabilization of the ionic structure can be realized by dimerization (LXXXVIIIe), since the ring makes it impossible sterically for the hydroxyl group of the enolized form to approach closely enough to the carbonyl oxygen of the same molecule to interact with it in the manner shown in formula LXXXVIIIc. These steric effects can be described as instances in which, according to Bredt's rule, chelation of the enol form of the cyclic diketones is not possible unless the ring size of the diketone is large, since the bridged-ring chelate structure LXXXVIIIc has bridgehead double bonds. Thus the shift in absorption spectrum on dilution may not be characteristic of large-ring cyclic β-diketones where Bredt's rule allows a bridgehead double bond.



LXXXVIIIc: Y = H or metal



LXXXVIIId



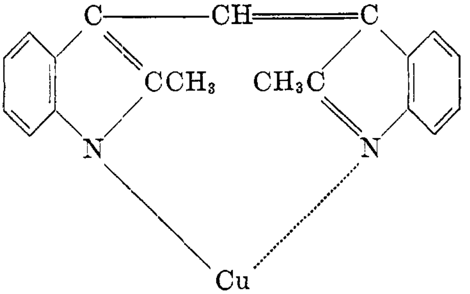
$$\begin{array}{ccccccc}
\mathrm{CH_2} & \text{—} & \mathrm{C} & \text{—O—H—O=} & \mathrm{C} & \text{—} & \mathrm{CH_2} \\
| & & \| & & | & & | \\
\mathrm{(CH_3)_2C} & & \mathrm{CH} & & \mathrm{CH} & & \mathrm{C(CH_3)_2} \\
| & & | & & \| & & | \\
\mathrm{CH_2} & \text{—} & \mathrm{C} & \text{=O—H—O—} & \mathrm{C} & \text{—} & \mathrm{CH_2}
\end{array}$$

LXXXVIIIe

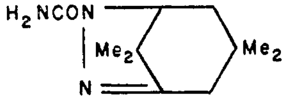
Weygand and Forkel (185) prepared beryllium and aluminum salts of 5,5-dimethyl-1,3-cyclohexanedione (dimedon) by exchange with the corresponding metal derivatives of ethyl acetoacetate. They found the properties of these cyclic β-diketone derivatives to be entirely different from those of the open-chain β-diketones. These salts melted with complete decomposition at temperatures near 300°C., they could not be distilled in high vacuum but rather decomposed, and they were not soluble in inert solvents such as benzene and chloroform. Solution occurred transitorily in methanol or ethanol but solvolysis took place to regenerate dimedon. They dissolved in ethyl acetoacetate but in doing so gave the chelate derivative of the ester and free dimedon. Molecular weight determinations could not be made, owing to insolubility in suitable solvents. Weygand and

Forkel pointed out the necessity for spatial proximity of the two oxygen atoms in order to obtain the typical chelate derivatives LXXXVIIIb, and they attributed the difference in behavior of the open-chain and the dimedon metal derivatives to the fixation of the two carbonyl groups in the cyclohexane ring. According to Bredt's rule, one would expect that normal chelate metal derivatives could not be obtained from monocyclic 1,3-diketones, except those having large rings, because these derivatives (LXXXVIIIc) would be bridged-ring structures with bridgehead double bonds. Similarly, the proposed chelate structure LXXXVIIIf (56) seems inconsistent with Bredt's rule.

Methylation of dimedon gave a mixture containing 2,2,5,5-tetramethyl-1,3-cyclohexanedione, whose disemicarbazone was reported by Hirsjärvi (75) to be converted on heating to the pyrazoline derivative LXXXVIIIg. The product was a high-melting (325°C.), highly insoluble material which could not be purified, and its structure was not proved. While open-chain 1,3-diketones form heterocyclic derivatives by reaction with amidines (forming pyrimidines), with hydrazine or its derivatives (forming pyrazoles), or with hydroxylamine (forming isoxazoles, from monoöximes), the formation of analogous heterocyclic compounds (including LXXXVIIIg) from monocyclic 1,3-diketones with relatively small rings would be hindered, according to Bredt's rule, since the expected bridged-ring products would have bridgehead double bonds. It has been pointed out (145) that dioximes can be obtained from monocyclic 1,3-diketones but not from the open-chain type, since with the latter the formation of isoxazoles is preferred.



LXXXVIIIf

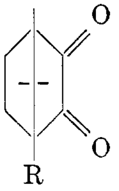


LXXXVIIIg

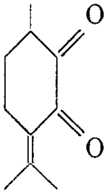
3. Camphorquinone and camphenilone

When camphorquinone (LXXXIXa) was treated with sulfuric acid an isomeric product was obtained which Manasse and Samuel (103) considered to have the enolic structure LXXXIXc. Bredt, Rochussen, and Monheim (42), at a time before Bredt's rule had been described, regarded this structure as unlikely in view of an analogous instance in which camphor underwent bridge cleavage. This reinvestigation showed that the product obtained was the monocyclic compound XC. This reaction was cited by Bredt (44) in support of the rule.

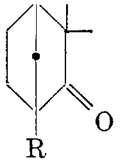
Bredt and Doerenkamp (37) attempted the bromination of camphorquinone to obtain LXXXIXb, by analogy with the bromination of camphor, but they were not successful. Likewise, Bredt-Savelsberg (45) was unable to obtain XCIb by the bromination of camphenilone (XCIa). Considering the bromination of ketones to occur by the addition of bromine to the enol form, Bredt (44) accounted for the failure of these brominations to occur because, according to the rule, these ketones cannot enolize.



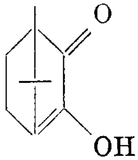
LXXXIXa: R = H
LXXXIXb: R = Br



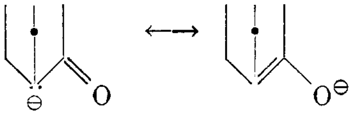
XC



XCIa: R = H
XCIb: R = Br
XCIc: R = CH_3



LXXXIXc



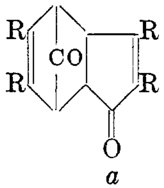
XCII

Ruzicka (136) indicated that a hypothetical synthesis of fenchone (XCIc) by Haller–Bauer methylation of camphenilone (XCIa) at the bridgehead position is not operable, since at ordinary temperatures XCIa on steric grounds would not react with sodium amide to form the enolate anion, while at higher tempertures it has been found by Semmler (149) that cleavage occurs to form (after hydrolysis) 3-isopropylcyclopentanecarboxamide. The steric reason for the failure of XCIa to form the enolate anion might be described in the same way as Bartlett and Woods (24) explained the non-enolic character of bicyclo[2.2.2]-2,6-octadione (LXXXVIa) (page 249). That is, resonance stabilization as shown in formula XCII is inhibited according to Bredt's rule. Similarly Allen, Jones, and Van Allan (5) found that camphorquinone (LXXXIXa) in the Zerewitinoff analysis showed two additions with methylmagnesium iodide but no evolution of methane (active hydrogen).

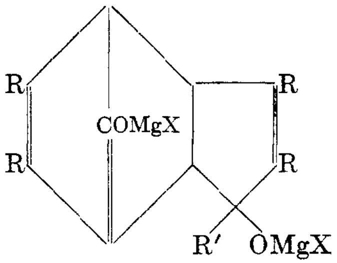
The failure of these compounds to enolize was further shown by their nonexchange with deuterium. Nesmeyanov and coworkers (113) reported that the α-hydrogens of camphorquinone and camphenilone failed to exchange with deuterium when these compounds were heated in an autoclave with dioxane–heavy water containing potassium hydroxide for 70 hr. at 130–135°C., while simpler ketones readily underwent the exchange. They considered the nonexchange to be due to the failure of these bridged-ring ketones to enolize, according to Bredt's rule.

4. Substituted bicyclo[2.2.1]-2-hepten-7-one system

Allen and coworkers (3, 4) found that XCIII reacted with 2 moles of Grignard reagent in the Zerewitinoff determination, showing one addition and one active hydrogen. They attributed this result to addition at carbonyl *a* and enolization at the carbonyl bridge as shown in XCIV. This structure was assumed because hydrolysis of the addition complex regenerated a monocarbinol which showed thermal decarbonylation, a reaction which they had found characteristic of



XCIII: R = C_6H_5



XCIV: R = C_6H_5; R′ = CH_3

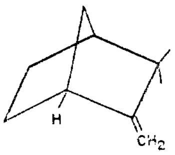
carbonyl bridge compounds having the bicyclo[2.2.1]-2-hepten-7-one structure. In later work (7), however, they found this assumption involving a supposed exception to Bredt's rule to be no longer tenable. They examined the analogous compound camphorquinone, suggested by Woodward, and found that it showed addition but no enolization with the Grignard reagent (*cf.* page 253). The structure then favored for the magnesium enolate was one in which one of the rings was opened.

5. Triptycene

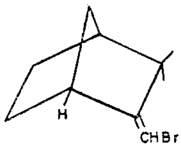
The activity of the "methyl" hydrogen in triptycene (XIXb) and in triphenylmethane parallels the reactivity of the corresponding halogen compounds, the bridged-ring structures being considerably less active. Bartlett, Ryan, and Cohen (23) found that triptycene gave no exchange with phenylisopropylpotassium under conditions which lead to immediate reaction in the case of triphenylmethane; that triptycene was not chlorinated by sulfuryl chloride in the presence of benzoyl peroxide, whereas toluene under identical conditions gave a high yield of benzyl chloride; and that chromic anhydride under conditions which lead to the formation of triphenylmethylcarbinol from triphenylmethane formed only anthraquinone and carbon dioxide from triptycene. They considered that to the extent that the central hydrogen in triphenylmethane is activated by the possibility of resonance in the triphenylmethide ion, such activity should be diminished or absent in triptycene. Forms such as XXI (page 230) should be unimportant, according to Bredt's rule, in stabilizing the anion, cation, or free radical from triptycene.

6. Camphene

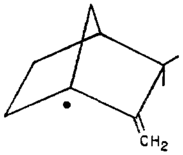
In examining the scope of *N*-bromosuccinimide as a brominating reagent for allylic positions Roberts and Trumbull (134) investigated its reaction with camphene (XCV) in which the only allylic hydrogen is at a bridgehead. They pointed out that form XCVIb would not be expected to contribute to the resonance stabilization of the free-radical intermediate XCVIa, and that if such resonance stabilization is necessary the allylic bromination of camphene with this reagent should be difficult or impossible. The product obtained from *N*-bromosuccinimide and camphene was a mixture of bromides of which the principal (65 per cent) component was 8-bromocamphene (XCVII) and there was no indication of the presence of the bridgehead halide. Bromination of bicyclo-[2.2.1]-2-heptene (norbornylene) similarly did not give the bridgehead (allylic) derivative (135). Roberts and Trumbull pointed out the failure to accomplish related reactions with triptycene (*cf.* page 254).



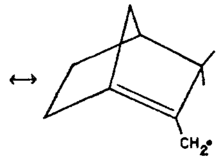
XCV
Camphene



XCVII
8-Bromocamphene



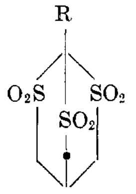
XCVIa



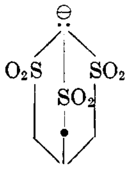
XCVIb

7. *Bicyclic trisulfone*

Doering and Levy (59) prepared the bicyclic trisulfone XCIXa in an investigation of the acidity of hydrogen alpha to the sulfone group. This compound was found to dissolve in aqueous sodium bicarbonate without decomposition, while its 1-methyl homolog (XCIXb) was insoluble even in sodium hydroxide solution. A close comparison with the work of Bartlett and Woods (24) on bicyclo[2.2.2]-2,6-octadione (page 249), however, was not possible. They considered that the



XCIXa: R = H
XCIXb: R = CH_3



C

stabilization of the negative charge in the anion C by the inductive effect of the adjacent groups would be unaffected by the steric configuration of the trisulfone. On the other hand, resonance involving orbitals of the sulfur might not be inhibited if such hybridization allows the use of octahedral bond angles. Thus Doering and Levy suggested that Bredt's rule may not apply to C═S, but since the question of the occurrence of an actual carbon–sulfur bond is unsettled, it is not certain how Bredt's rule applies in this instance (2a, 72c).

E. ANHYDRIDE FORMATION

1. *Dehydrocamphoric acid*

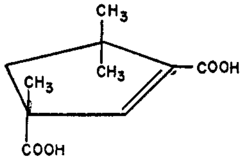
The failure of dehydrocamphoric acid (III) to form its anhydride and the rearrangement of the double bond to the position as in VI on forced dehydration have been discussed (page 220).

2. Dehydroisofenchocamphoric acid

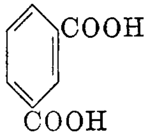
Toivonen (174) found that when dehydroisofenchocamphoric acid (Ca) was heated alone or was heated with acetyl chloride at 150°C. no monomeric anhydride could be obtained. He attributed this result to steric hindrance of the kind which prevents the formation of the anhydride of dehydrocamphoric acid (page 221). Using Bredt's terminology he described the carboxyl groups as being in the *meso-trans* position to one another as a consequence of the double bond and thus unable to come close enough together to form the anhydride. Bredt (44) cited this work in support of the rule. In this structure there is no other position available for the migration of the double bond to permit a reaction analogous to the one which occurs with dehydrocamphoric acid (III).

3. Isophthalic acid and its hydro derivatives

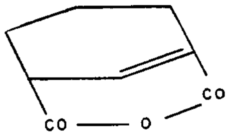
In discussing the anhydride formation of dehydrocamphoric acid Bredt, Houben, and Levy cited isophthalic acid (CII), which does not form an anhydride, and hexahydroisophthalic acid (presumably the *cis* form), which readily gives one. Perkin and Pickles (119, 120) had reported that of the three position isomers of tetrahydroisophthalic acid, only CIIIa forms an anhydride and that CIIIb and CIIIc when treated with acetic anhydride give the same anhydride as CIIIa by a rearrangement of the double bond. Bredt (35) objected to this conclusion, since in the derivative of CIIIa, i.e., CIV, a double bond occurs at the bridgehead of a small atomic-bridged-ring system. Bredt compared the steric situation in structure CIV with the simpler hypothetical monocyclic anhydride of the fumaric acid-like forms of methylglutaconic acid and concluded that CIIIa could not form an internal anhydride. Further investigation by Farmer and Richardson (61, 62), who did not refer to Bredt's paper (35) or to Bredt's rule, showed that the anhydride-forming isomer supposed by Perkin and Pickles to be the Δ^1 acid (CIIIa) is actually the *cis* Δ^4 acid (CIIIc), a result which is consistent with Bredt's rule. Bredt (35) proposed the generalization that an eight-membered oxygen-containing ring with a one-membered bridge in the 1,5-position, i.e.,



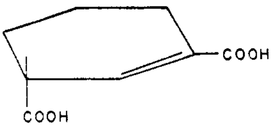
Ca



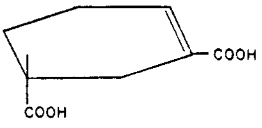
CII
Isophthalic acid



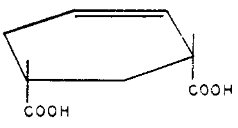
CIV



CIIIa



CIIIb

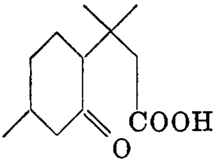


CIIIc

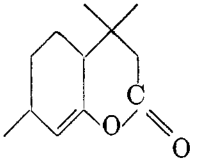
a [3.3.1] system, cannot be formed when a double bond occurs at a bridgehead (*cf.*, however, page 244).

F. ENOL LACTONIZATION OF γ- AND δ-KETO ACIDS

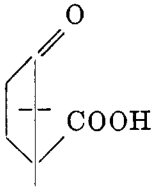
Vorländer (176) reported that the monocyclic compound pulegoneacetic acid (CV) when heated at 115°C. slowly loses water to form the bicyclic valence-bridged-ring enol lactone CVI (or isomer with double bond common to both rings). With camphononic acid (CVII), however, an analogous reaction would lead to CVIII with a double bond at a bridgehead in a small atomic-bridged-ring structure. CVII, m.p. 228°C., was found to sublime or distill in the temperature range 260–290°C. without dehydration or other decomposition. Windaus and Bohne (193) described the hindrance of the reaction leading to this enol lactone by applying Bredt's rule to the expected product. Bredt's rule was also used by Windaus and Bohne in interpreting the behavior of some keto acids obtained in the degradation of steroids. Although later work has revised some of these structures, they made a reasonable generalization based on Bredt's rule that enol lactones would not be obtained from the cyclohexanonecarboxylic acids, and that with cyclohexanoneacetic acids such products would be formed only from the "ortho" or 2-acetic acid derivatives.



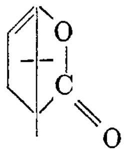
CV
Pulegoneacetic acid



CVI

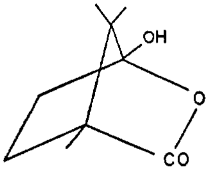


CVII
Camphononic acid



CVIII

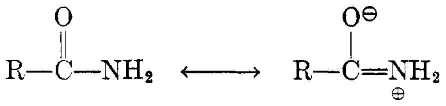
If the mechanism of enol lactone formation involves the dehydration of a lactol intermediate (152) such as CIX, then the dehydration step is evidently the hindered process (*cf.* Section B,1, page 235).



CIX

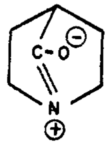
G. FORMATION AND REACTIONS OF LACTAMS

Considering the double-bond character (CX) of the C—N bond in amides, Lukeš (102) applied Bredt's rule to the bicyclic structures CXI, CXIIa, and CXIIb, which he concluded, according to the rule, probably cannot be formed.

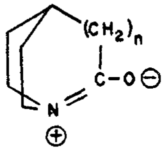


$$R{-}\overset{O}{\overset{\|}{C}}{-}NH_2 \longleftrightarrow R{-}\overset{O^{\ominus}}{\overset{|}{C}}{=}\underset{\oplus}{NH_2}$$

CX

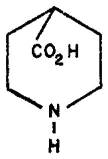


CXI

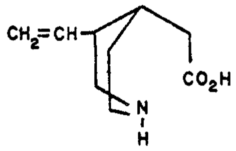


CXIIa: $n = 1$
CXIIb: $n = 2$

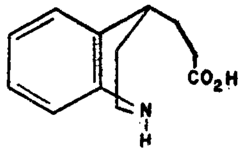
In this way he accounted for the failure of CXIII to lactamize even when heated above 300°C. The similar behavior of meroquinene (CXIV), m.p. 236°C., which underwent decomposition without giving the bicyclo[2.2.2]lactam, and of CXV, which did not cyclize, were also interpreted in this way. Lukeš pointed out that these compounds which he described as sterically "impossible," might be prepared some time by another procedure but if they were made they would have an actual carbonyl group with properties different from those which we recognize as characteristic of amides.



CXIII

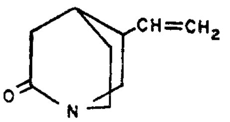


CXIV
Meroquinene

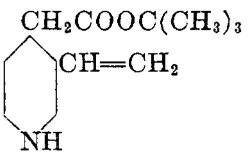


CXV

In studying the autoxidation of quininone with oxygen in the presence of potassium *tert*-butoxide Doering and Chanley (58) attempted to isolate an intermediate cleavage fragment CXVI, but only the product (CXVII) of further cleavage was found. They too considered the unknown type of bicyclic amide



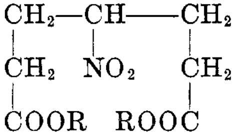
CXVI



CXVII

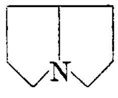
with nitrogen as the bridgehead to be more reactive than ordinary amides and quoted Woodward's interpretation of this reactivity: "The atoms attached to the carbon of the carbonyl and to the nitrogen atom at the bridgehead cannot attain coplanarity and consequently normal amide resonance, which involves some double bond character for the C—N link, will be inhibited. Accordingly amides of this type would be expected to exhibit the reactive properties of a more or less isolated carbonyl group."[4]

Leonard and coworkers (93, 94) developed a method for the preparation of pyrrolizidines (CXIX) from γ-nitropimelic esters (CXVIII) by two-step catalytic hydrogenation, first with platinum oxide at low pressure and then with copper chromite at high temperature and pressure. They considered that, following the reduction of the nitro group, bicyclic amide intermediates were formed which were then further reduced to the bicyclic amine. Attempts by Leonard and Shoemaker (95) to prepare the atomic-bridged-ring amine CXX by reduction of CXXIa or CXXIb, however, were not successful. While the amide intermediates in the preparation of pyrrolizidines are valence-bridged-ring compounds, the analogous ones from CXXIa or CXXIb would have atomic-bridged-rings with nitrogen as the bridgehead like the structures discussed above. Thus the failure to obtain CXX may have been due in part to the hindrance according to Bredt's rule of reactions leading to the atomic-bridged-ring amide intermediates.

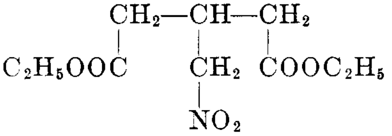


$$\begin{array}{lll} CH_2— & CH— & —CH_2 \\ | & | & | \\ CH_2 & NO_2 & CH_2 \\ | & & | \\ COOR & & ROOC \end{array}$$

CXVIII

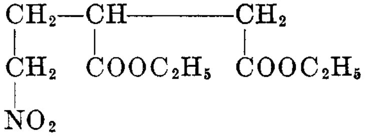


CXIX



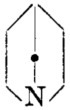
$$\begin{array}{llll} & CH_2— & CH— & CH_2 \\ & | & | & | \\ C_2H_5OOC & & CH_2 & COOC_2H_5 \\ & & | & \\ & & NO_2 & \end{array}$$

CXXIa



$$\begin{array}{lll} CH_2— & CH— & —CH_2 \\ | & | & | \\ CH_2 & COOC_2H_5 & COOC_2H_5 \\ | & & \\ NO_2 & & \end{array}$$

CXXIb



CXX

Woodward (202) pointed out that the amide link in β-lactams, and particularly in penicillin, should not be normal. With simple β-lactams the ratio of the contributions of the two forms CXXIIa and CXXIIb will differ from that with normal

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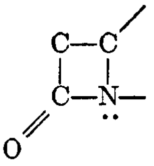
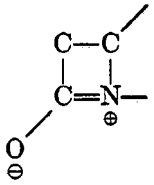
[4] Albertson (1a) has recently reported the synthesis of the bicyclic amide 5-carbethoxy-9-methyl-2-oxo-1-azabicyclo[3.3.1]nonane. It would seem that normal amide resonance in this [3.3.1] system would be somewhat hindered, with a consequent decrease in stability as compared with ordinary amides.

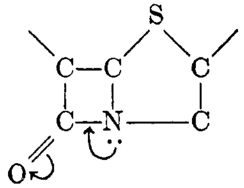
amides, the latter contributing less since the introduction of the double bond into the cyclobutane ring will be somewhat opposed by strain set up as a consequence of angular distortions. In penicillin Woodward considered that this effect should be considerably magnified, since here the normal displacement shown in the partial structure CXXIII confers partial double-bond character on a link at the "bridgehead" of a small nonplanar bicyclic system. This effect was explained alternatively by applying Bredt's rule, according to which the resonance stabilization described above would be damped. Like biphenylene (CXXIV) (14), CXXIII is a valence-bridged-ring (fused-ring) structure rather than an atomic-bridged-ring one, and although these compounds are clearly strained they are regarded as outside the scope of Bredt's rule (page 222).



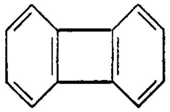
CXXIIa



CXXIIb



CXXIII



CXXIV
Biphenylene

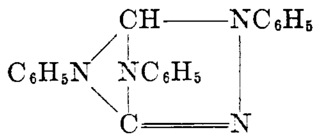
H. MISCELLANEOUS STRUCTURES

In addition to the examples described above other structures have appeared in the literature which are pertinent to Bredt's rule. No attempt has been made to obtain a complete list, but the following additional ones are included here.

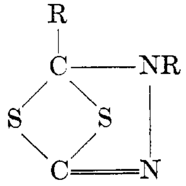
1. Bicyclic systems

(a) [2.1.1] Ring system: nitron

Wittig (197b) considered it surprising, in view of Bredt's rule, that nitron was regarded as having structure CXXIVa. Schönberg (146) reëmphasized the stereochemical difficulty according to this rule of forming structures like CXXIVa

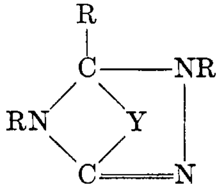


CXXIVa

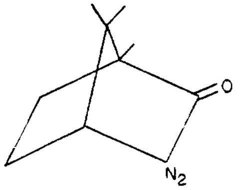


CXXIVb

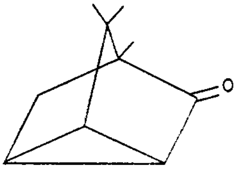
and proposed an alternative structure for nitron. He also called attention to the fact that the generally accepted structures CXXIVb and CXXIVc for several heterocyclic compounds do not conform to Bredt's rule and suggested other structures for compounds of this kind. Sidgwick (154) referred to CXXIVa as sterically improbable.



CXXIVc: Y = O, S



CXXV
Diazocamphor

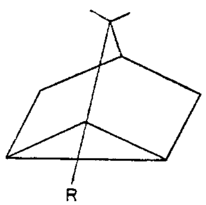


CXXVI

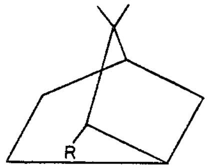
(b) [2.2.1] Ring system

(*1*) *Diazocamphor.*—Angeli (8) reported the product obtained on thermal decomposition of diazocamphor (CXXV) to be the unsaturated bicyclic ketone XXIV (page 231). Bredt and Holz (38) considered this structure improbable according to Bredt's rule, and their reinvestigation showed that the material was actually a saturated tricyclic ketone (CXXVI), a derivative of cyclene. 2-Diazocamphane was reported by Heubaum and Noyes (73) to give a similar cyclization product (cyclene), and Wilson (191) found that dehydrobromination of bromoisocamphenilanic acid (structure LII, page 237, with Br replacing OH) with aqueous sodium carbonate gave tricyclenic acid rather than an unsaturated acid as had been previously reported.

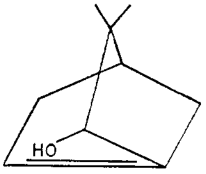
(*2*) *Apotricyclenol.*—Lipp and Padberg (99) considered that the tertiary alcohol apotricyclenol (CXXVIIa), an analog of cyclopropanol, should readily undergo ring-cleavage and rearrangement reactions, but that formation of CXXVIId by a reaction analogous to the observed conversion of cyclopropylamine to allyl alcohol would be prevented, according to Bredt's rule. When CXXVIIa was heated alone or with hydrochloric acid, camphenilone (CXXVIIIa) was obtained, the reaction resembling the reported transformation of ω-aminotricyclene hydrochloride (CXXVIIb) to camphenilanaldehyde (CXXVIIIb) and of tricyclene (CXXVIIc) to camphene (CXXVIIIc) *via* camphene hydrochloride.



CXXVIIa: R = OH
CXXVIIb: R = $CH_2NH_2 \cdot HCl$
CXXVIIc: R = CH_3

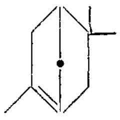


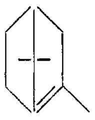
CXXVIIIa: R = =O
CXXVIIIb: $R = \begin{cases} CHO \\ H \end{cases}$
CXXVIIIc: R = $=CH_2$

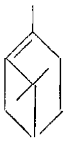


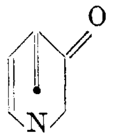
CXXVIId

(3) *Others.*—Bredt, Thouet, and Schmitz (44) considered structures CXXIX and CXXX, which Bartelt proposed for fenchene, to be improbable. γ-Pinene was believed by Wallach and Blumann (179) to be CXXXI, but it has been pointed out (168a) that this structure is sterically impossible, according to Bredt's rule. Ochiai and Ikuma (108, 114) tentatively suggested CXXXIIa as one possible structure for a product obtained in the Houben–Hoesch self-condensation of *N*-cyanomethylpyrrole. The molecular weight of the material, m.p. 307–308°C., could not be determined because of insolubility, however, and proof of structure was not undertaken.

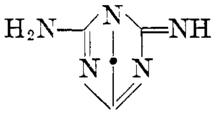

CXXIX


CXXX


CXXXI

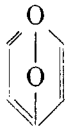


CXXXIIa

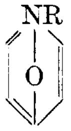


CXXXIIb

Slotta and Tschesche (156) assumed structure CXXXIIb for a compound formed by the reaction of ethyl chloroacetate and biguanide. Structures suggested for γ-pyrones (CXXXIIc) (15, 48) and for *N*-substituted γ-pyridones (CXXXIId) (159), in addition to their valence difficulties, are not consistent with Bredt's rule.



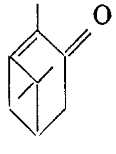
CXXXIIc



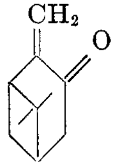
CXXXIId

(c) [3.1.1] Ring system: carvopinone

A product designated carvopinone was obtained by Wallach and Engelbrecht (180) on heating nitrosopinene with aqueous oxalic acid. The material was unstable and was not obtained in a pure state, since it was found to be readily converted to the monocyclic compound carvone (2-methyl-5-isopropenyl-2-cyclohexenone). They considered (180, 181) carvopinone to be CXXXIV, being derived from nitrosopinene which they thought to have the older structure XXXV (page 233). Ruzicka and Trebler (141), however, showed the structure of nitrosopinene to be XXXVII (*cf.* page 233). Structure CXXXIV for carvopinone was evidently accepted even quite recently (3, 68, 82, 137, 140, 155c, 160, 161), although it is in disagreement with Bredt's rule. Schmidt (81e, 143, 144, 155c) recently reported that the product commonly called carvopinone is really pinocarvone, having structure CXXXV, and that the material commonly described as pinocarvone is actually the aldehyde myrtenal. He suggested that the



CXXXIV

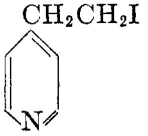


CXXXV

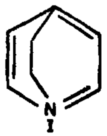
name carvopinone and the structure CXXXIV be disregarded.

(d) [2.2.2] Ring system

Löffler and Stietzel (101) investigated the synthesis of bicyclic amines by reduction and intramolecular alkylation of 2-(δ-iodobutyl)pyridine and 4-(β-iodoethyl)pyridine (CXXXVI). While 2-(δ-iodobutyl)pyridine gave the bicyclic valence-bridged-ring derivative, unsatisfactory results were obtained in making quinuclidine from CXXXVI. The pyridinium salt of CXXXVI was written as



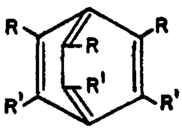
CXXXVI



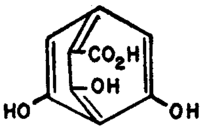
CXXXVII

CXXXVII, although no conclusive evidence for this monomeric structure was obtained. This representation was later shown (107) to be incorrect, since the product obtained was polymeric, a result of intermolecular rather than intramolecular salt formation.

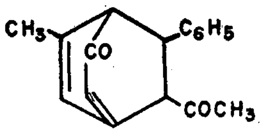
Leuchs and Simion (96) reported structures CXXXVIII and CXXXIX for by-products obtained in the preparation of phloroglucinol derivatives.



CXXXVIII: R = $COOC_2H_5$
R' = $OCOCH_3$

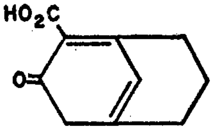


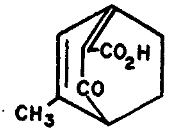
CXXXIX

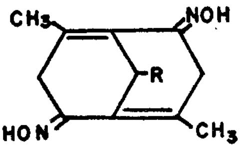


CXL

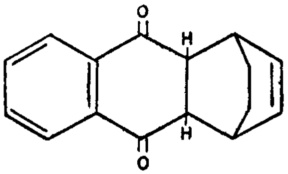
The condensation of benzaldehyde with 2 moles of acetylacetone followed by removal of 2 moles of water with ethanolic hydrochloric acid yielded a diketone, and CXL was considered (86) as one of three possible structures for this product. Knoevenagel and Mottek (87) regarded CXLIa or CXLIb as a possible structure for the cyclization product of ethyl 3-methyl-2-cyclohexenylidenecyanoacetate. Mohr (110) pointed out that these structures are contrary to Bredt's rule and are therefore open to question. Structure CXLIc considered (86) for the dioxime formed from 4,6-diacetyl-3-methyl-5-phenyl-2-cyclohexenone and hydroxylamine also is inconsistent with Bredt's rule.

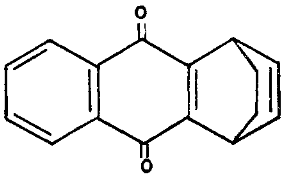

CXLIa

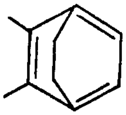

CXLIb


CXLIc: R = C_6H_5

On mild dehydrogenation CXLII was found to lose only two hydrogens to form CXLIII. Diels and Alder (57) considered this reaction to show that Bredt's rule is valid for a two-membered bridge as well as for the one-membered bridge in the pinane and camphane series, since aromatization would lead to the improbable structure shown partially in CXLIV. Aromatization does occur on heating CXLIII, but the bridge is eliminated in the process.

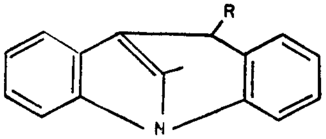

CXLII

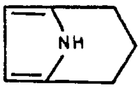

CXLIII

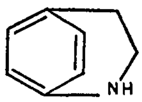

CXLIV

(e) [3.2.1] Ring system

Structures CXLV, where R is a keto or a bis(β-indolyl)methyl radical (172, 173), are inconsistent with Bredt's rule. The diethyl ester of *N*-methyl-2,5-pyrrolidinediacetic acid was found to undergo a Dieckmann condensation to a tropane derivative but the corresponding pyrrole derivative did not. Willstätter and Bommer (189) called attention to the fact that this reaction is hindered for spatial reasons, since the expected product (CXLVI) would be extraordinarily strained because of the distortion of valence bonds. By comparison, they considered that benzene cannot have a meta or para bridge containing two or three carbon atoms, and accordingly the identity of Braun's reported "dihydro-*p*-indol" (CXLVII) was questioned.

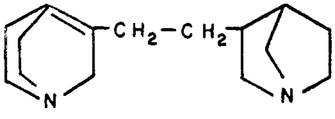

CXLV


CXLVI

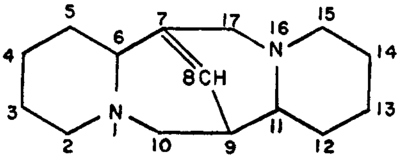

CXLVII

(f) [3.3.1] Ring system

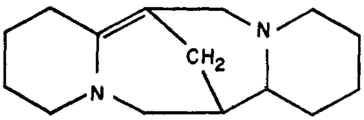
(*1*) *Spartein derivatives.*—Two different isomeric bases, $C_{15}H_{24}N_2$, derived from spartein, $C_{15}H_{26}N_2$, have been reported, one by Willstätter and Marx (190), designated spartyrin, and the other by Wolffenstein and Reitman (198), named dehydrospartein. Wolffenstein and Reitman suggested structure CXLVIII for dehydrospartein, based on the currently used structure of spartein, but Schöpf and Braun (147) objected to this in view of Bredt's rule. Winterfeld and Schirm (196) reviewed the above work, including that of Schöpf and Braun, and from their oxidative degradation studies, together with the structure since suggested for spartein, proposed structure CXLIX for dehydrospartein and CL for Willstätter and Marx's isomeric spartyrin. Prelog, Ruzicka, Barman, and Frenkiel (127) considered it improbable that Bredt's rule should not apply to these nitrogen analogs of bicyclo[3.3.1]nonane written by Winterfeld and Schirm. In a later paper, however, Winterfeld and Besendorf (194) accepted the position of the double bond in the [1] branch of the [3.3.1] system (CXLIX) as unlikely in view of Bredt's rule, as Prelog had pointed out (194), but they did not refer to CL, in which the double bond is in one of the [3] branches. Winterfeld and Rönsberg (195) had considered structures for didehydrospartein having double bonds in (*a*) the 4,5- and 11,12-positions and (*b*) the 4,5- and 9,11-positions, but Winterfeld and Besendorf (194) indicated that both of these structures agree with Bredt's rule. The rule, however, is regarded as prohibiting any bridgehead double bond in the central [3.3.1] system, i.e., in the 6,7-, the 7,8-, or the 7,17-position (CXLIX) or the other corresponding locations. Beyler (27) has apparently reëxamined the structures of these unsaturated bases.



CXLVIII

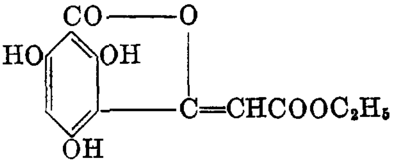


CXLIX

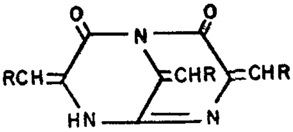


CL

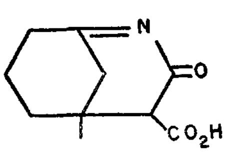
(*2*) *Others.*—Jerdan (80) wrote the meta-bridged phloroglucinol structure CLI for the product obtained by the reaction of sodium with acetonedicarboxylic ester. In view of its strong acidity Leuchs and Sperling (97, 159) suggested, however, that the product obtained was actually a hydroxycoumarin derivative, although no reference was made to Bredt's rule. On treating the azlactone of acetyldehydrophenylalanyldehydrophenylalanyldehydrophenylalanine with sodium hydroxide, Tietzman, Doherty, and Bergmann (170) obtained a product, having the composition $C_{27}H_{19}O_2N_3$, for which structure CLII appeared more probable to them than two isomeric bicyclic systems. The latter were also bridged-ring structures with bridgehead double bonds. When ethyl (1-methyl-3-ketocyclohexyl)cyanoacetate was heated with 15 per cent hydrochloric acid, an acidic compound was formed to which Farmer and Ross (63) assigned structure CLIII. Barltrop (16) observed that this structure is improbable for several reasons, including the fact that it violates Bredt's rule. Vaughan (175) pointed out that structures CLIVa and CLIVb, which had been proposed by other workers, embody flagrant contradictions of Bredt's rule.



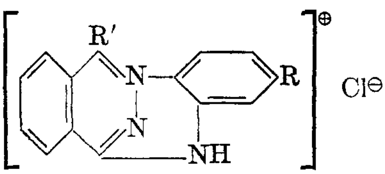
CLI



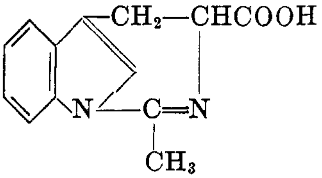
CLII: R = C_6H_5



CLIII



CLIVa: R′ = H
CLIVb: R′ = CH_3

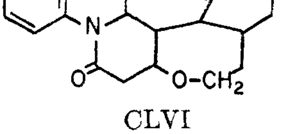


CLV

(g) [4.2.1] Ring system

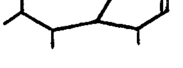
A compound formed from acetyl chloride and tryptophan was believed by Wrede and Feverriegel (203) to be CLV.

2. Complex ring systems



CLVI

CLVII



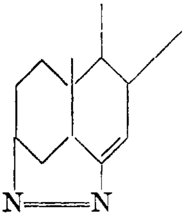
CLVIII

(a) Strychnine and neostrychnine

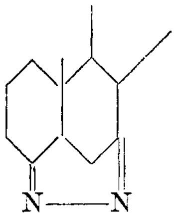
In discussing the structure of strychnine, Woodward (199) regarded structure CLVI as sterically impossible. Prelog and Häfliger (126) used Bredt's rule to account for the low basicity of neostrychnine (shown partially in CLVII), in which the double bond is in the α,β-position to the nitrogen. Adams and Mahan (1) reported that vinyl tertiary amines in general exhibit stronger basicities than the corresponding saturated compounds, and they explained this by assuming conversion to the quaternary ammonium hydroxide. Prelog and Häfliger considered that the low basicity of neostrychnine (*cf.* CLVII) is due to the steric hindrance, according to Bredt's rule, of the formation of the quaternary ion shown partially in CLVIII.

(b) Steroid diketone derivatives

A procedure commonly used in characterizing steroid 1,4-diketones is their reaction with hydrazine. The resulting products have usually been regarded (65, 165, 192) as pyridazine derivatives, by analogy with the behavior of open-chain 1,4-diketones. Fernholz (65) concluded from steric considerations that the double bonds must be in the positions shown in the partial structure CLIX, and he pointed out that structures with the double bonds in other positions could not be constructed with models. Double bonds in the positions shown in CLX (115) would presumably involve considerable strain.



CLIX

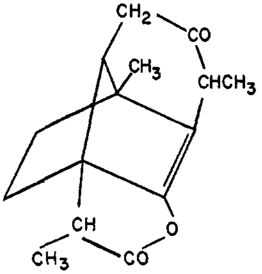


CLX

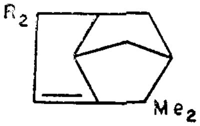
In some instances it has been reported (103a, 113a, 165) that the derivatives obtained are actually polymeric, and therefore that the formation of a "product" from hydrazine and the diketone does not constitute proof of the 1,4-positions of the carbonyl groups. Similarly, Windaus (192) found that cholestanedione and ammonia gave a product which appeared to result from a dehydration reaction involving 2 moles of the diketone and 1 mole of ammonia, rather than a pyrrole derivative as is formed with open-chain 1,4-diketones. If one regards CLIX and CLX as modified bicyclo[6.2.2] systems, the double-bond arrangement CLIX preferred by Fernholz contains one bridgehead double bond in the [6] branch, while the alternative structure CLX has two bridgehead double bonds in one of the [2] branches. Models indicate CLX to have considerable strain, in contrast to CLIX.

(c) Others

Woodward and Kovach (201) considered the enol-lactone structure CLXI for the santonides incorrect, since it possesses a carbon–carbon double bond in an impossibly strained position at the bridgehead in a bicyclo[3.2.1]octane ring system. Their further investigation of these products supported a different enol-lactone structure in which such strain is not present.

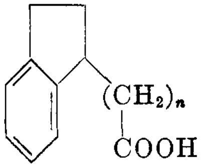


CLXI

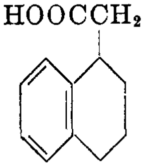


CLXII: R = C_6H_5

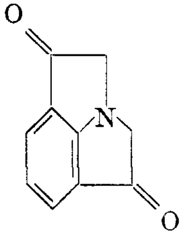
Lipp and Quaedvlieg (100) treated ω-benzoylcamphene with phenylmagnesium bromide and, while not able to isolate the expected tertiary carbinol, obtained a hydrocarbon, $C_{23}H_{24}$, which was found by quantitative hydrogenation to contain one double bond. They considered structure CLXII to be the most probable one for this compound but could not confirm this by oxidation. These authors concluded the spatial model of CLXII to be entirely possible from the standpoint of strain theory. They interpreted Bredt's rule as not applying to CLXII directly, and cited reference 34, in which Bredt presented a somewhat misleading picture of the ring size necessary for a bridgehead double bond (*cf.* page 244). Asahina and Sano (11) reinvestigated this work and were unable to obtain the hydrocarbon described above, but Bredt's rule was not mentioned. There is evidence, e.g., the data of table 1, that a bridgehead double bond cannot occur in the related (compare page 224) bicyclo[3.2.1] system in accordance with the rule, and it seems improbable that structure CLXII can be either essentially strainless or correct.



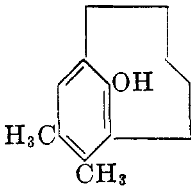
CLXIIIa: $n = 1$
CLXIIIb: $n = 2$



CLXIV



CLXV



CLXVI

Hückel (77) called attention to the fact that the somewhat strained ring system XVa (page 224) is as yet unknown. Attempts to cyclize CLXIIIa *via* the acid chloride were unsuccessful, although the next higher homolog CLXIIIb and CLXIV yielded the expected tricyclic ketones (32a). The formation of CLXV by a similar route apparently did not occur (78). The analogous bicyclic structure CLXVI was obtained in the dimethylphenol series (page 243); with the nitro substituent the keto form having one bridgehead double bond was reported (page 242).

The author is indebted to Dr. A. C. Cope of the Massachusetts Institute of Technology for encouraging his interest in this subject, and to Dr. J. D. Roberts of the Massachusetts Institute of Technology and Drs. T. L. Cairns, E. L. Jenner, and C. M. Langkammerer of the Chemical Department, du Pont Experimental Station, for their helpful suggestions and discussions during the preparation of the manuscript.

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