

DISPLACEMENT REACTIONS AT BRIDGEHEADS OF BRIDGED POLYCARBOCYCLIC SYSTEMS¹

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I. INTRODUCTION

A bridged ring system is defined as one in which two rings have three or more atoms in common. Those ring atoms which are bonded to three other ring atoms are called bridgehead atoms. Bridgehead displacements will be taken to include all reactions in which one atom attached to a bridgehead *carbon* atom is replaced by another atom, regardless of mechanism, and in which the ring skeleton remains unaltered. The available literature to June, 1954, is covered in this review.

Since bridgehead displacements are of interest primarily for their mechanistic implications, they will be classified according to mechanism, though such classification becomes difficult where the mechanisms are unknown or uncertain.

It is a convenient simplification to consider that all bridgehead displacements must be either two-step processes in which the displacing atom arrives after the departing atom has gone, or one-step (concerted) processes in which the displacing atom becomes attached to the bridgehead at the same time that the departing atom leaves. In the former type of mechanism, there must be an intermediate cation, radical, anion, or double bond at the bridgehead. In the latter type, the reaction may be either an intramolecular cyclic process or a bimolecular second-order process. Possible examples of all of these reaction types will be considered.

Bridgehead displacements are of interest because of the information that they provide about the possible stereochemistry of the various displacement reactions. Because backside approach of the attacking reagent and inversion of configuration are prohibited at a bridgehead, reactions which can proceed only by inversion mechanisms cannot occur at bridgeheads.

It was first recognized by Bartlett (8) that bridgehead displacements can yield valuable information about the preferred conformations of cations, radicals, and anions of carbon, since the possible conformations of such bridgehead intermediates may be restricted by strain. Thus, a planar configuration of the bridgehead carbon and the three attached atoms cannot be obtained in a small bridged-

ring system without introduction of considerable strain. In addition, some knowledge of the relative importance of the various factors which stabilize intermediates, such as resonance, hyperconjugation, hybridization, solvation, and relief of strain, may be obtained, since these factors are differently affected by the unique structural situation prevailing at the bridgehead (5).

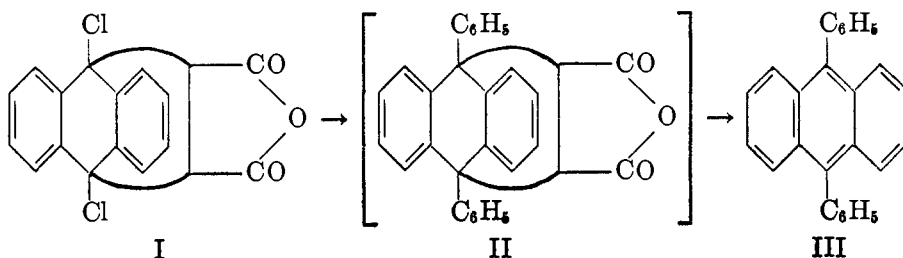
II. TWO-STEP DISPLACEMENT REACTIONS

A. BRIDGEHEAD CATIONS

The study of bridgehead carbonium-ion reactions has been particularly valuable in elucidating the factors important to carbonium-ion stability.

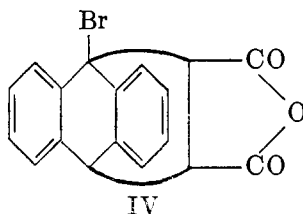
1. 9-Halo-9,10-dihydroanthracene-9,10-endo- α,β -succinic anhydrides

In 1931 Clar (17) found that I reacted with benzene and aluminum chloride to give 9,10-diphenylanthracene (III). He assumed an intermediate, II, which would have necessitated bridgehead cations in the initial Friedel-Crafts reaction. It has been pointed out, however, that a mechanism might be written involving



initial ring opening, and that the reaction therefore cannot be used as evidence for a bridgehead cation until II is shown to be a reaction intermediate (30).

It was later shown that carbonium-ion formation in similar systems was surprisingly difficult. Compound IV lost no bromide in 40 min. of boiling with alcoholic alkali (4), 18 hr. of boiling in 15–30 per cent potassium hydroxide (6), or 2.5 hr. of boiling and 3 days of standing in alcoholic silver nitrate. This is in striking contrast with the extreme reactivity normally observed in diarylmethyl

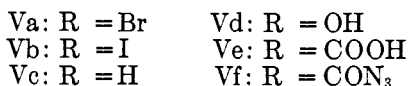
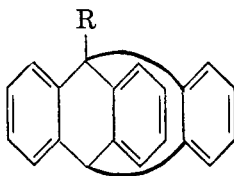


halides. Bartlett and Cohen (6) interpreted this result to mean that cations of the diarylmethyl type must be planar in order for resonance stabilization involving the aryl groups to be important. This means that the cationic carbon, the three attached carbons, and at least one of the benzene rings (50a) must lie in one plane or nearly so. Even if the three carbons attached to the bridgehead

carbon of the cation derived from IV became planar, the benzene rings would be held perpendicular to this plane and resonance thus inhibited.

2. Triptycyl halides

Later the similar compounds 1-bromotriptycene (Va) and 1-iodotriptycene (Vb) were prepared.

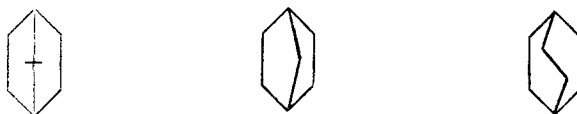


It was found that Va did not react with stannic chloride in boiling toluene in 12 hr. or with potassium hydroxide in refluxing ethanol in 5 days (9). Compound Vb failed to react with refluxing aqueous ethanolic silver nitrate in 48 hr. (7). Bartlett and Lewis (9) felt that this was probably another example of steric inhibition of resonance, but conceded that the hindrance of solvation at the bridgehead of the cation might be of comparable importance in determining its apparent instability, as had been pointed out by Winstein and Buckles (75a). Bartlett and Greene (7) pointed out also that there would be a considerable inductive effect due to the phenyl groups tending to destabilize the carbonium ion, and that a stiffening effect of the phenyl groups on the internal bond angles would have an additional destabilizing effect.

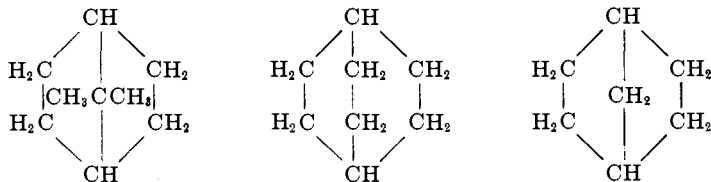
3. 1-Chloroapocamphane

Solvolysis-type reactions have also been studied in a number of cases uncomplicated by benzenoid resonance. Bartlett and Knox (8) prepared 1-chloroapocamphane (VIa)² to test a hypothesis that all nucleophilic substitutions

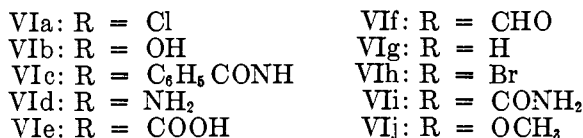
² In formulas of the following types, terminals and intersections of line segments represent carbon atoms bearing enough hydrogens to satisfy tetravalence:



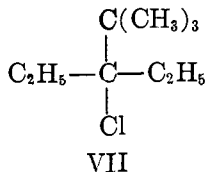
The complete representations of these structures are thus as follows:



involved one or more Walden inversions. They found that VIa gave no reaction



in 21 hr. of boiling with 30 per cent potassium hydroxide in 80 per cent ethanol or 48 hr. of boiling with aqueous ethanolic silver nitrate. This lack of reactivity is extreme when compared with the behavior of non-bridgehead tertiary chlorides. Bartlett and Knox considered the probable explanation of the unreactivity of VIa to be that carbonium ions must have planar configurations in order to be stable enough to be reaction intermediates. They cited the observation that trimethylborane (isoelectronic with the *tert*-butyl cation) is planar (41) and also stereochemical observations that indicated that carbonium ions must be either planar or oscillating rapidly between enantiomeric pyramidal forms. They felt that hindrance of solvation and the neopentyl character of VIa were probably relatively unimportant, because the open-chain analog VII solvolyzed in ethanol-water faster than *tert*-butyl chloride. Molecular models indicated that VII



would have little possibility for backside solvent participation.

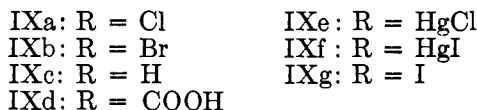
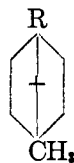
Bartlett and Knox estimated the strain energy for the 1-bicyclo[2.2.2]octyl cation (VIII) with a planar cationic carbon at the bridgehead to be 22.5 kcal., corresponding to a difference in rate of a factor of 10¹⁴ at 350°K. The strain energy in a planar apocamphyl cation was judged to be much greater.



VIII

4. 4-Halocamphanes

Doering and Schoenewaldt (24) found that although 4-chlorocamphane (IXa) was unreactive with bases under drastic conditions (potassium hydroxide in boiling ethanol for 2 days or sodium ethoxide at 205°C. for 2 days), it reacted

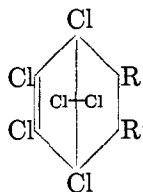


with aqueous silver nitrate at 205°C. to give an inseparable mixture of products. Likewise, aluminum bromide in refluxing cyclohexane and zinc chloride in butyl ether at 195°C. with IXa (C₁₀H₁₇Cl) gave inseparable hydrocarbon mixtures from which a saturated C₁₀H₂₀ fraction was obtained. A 50 per cent aqueous solution of zinc chloride at 195°C. gave an unsaturated oily product. The formation of a C₁₂H₂₂ cyclohexane dimer from the aluminum bromide reaction indicated the source of hydrogen in the C₁₀H₂₀ material. Since products were not identified, it was not concluded that bridgehead carbonium ions had been produced, but only that the bridgehead carbon was probably electron deficient in the reaction transition states.

4-Bromocamphane (IXb) shows a similar resistance to formation of the carbonium ion under mild conditions and is unaffected by treatment for 22 hr. with silver nitrate in 80 per cent ethanol at 100°C. (40).

5. Allylic bridgehead chlorides

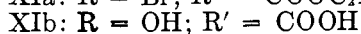
Resistance to attack by bases has also been observed in allylic bridgehead chlorides. Compound Xa was found (53) to yield no significant amount of ionic



chlorine on 6 hr. boiling with 10 per cent aqueous or alcoholic potassium hydroxide. Various other compounds of type X (exactly which compounds not specified) were found (26) to give up only 2-7 per cent of their total chlorine in 8 hr. of refluxing with 10 per cent alcoholic potassium hydroxide.

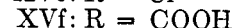
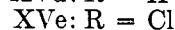
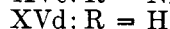
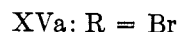
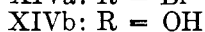
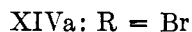
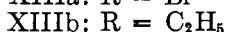
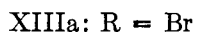
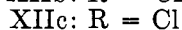
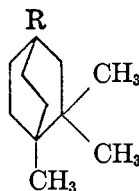
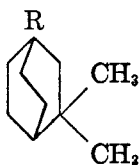
6. Bicyclo[2.2.2]octyl halides

In recent years, 1-substituted bicyclo[2.2.2]octane derivatives have been shown to undergo reactions involving bridgehead carbonium ions substantially more readily than with IV and V. Roberts, Moreland, and Frazer (64) found that XIa failed to react with silver oxide or silver nitrate in acetone-water mixtures, but was converted to XIb in 81 per cent yield by refluxing for 24 hr.



with 1 per cent sodium hydroxide. The negative carboxylate ion formed by saponification was thought to assist in the expulsion of bromide ion to form the carbonium ion.

Doering, Levitz, Sayigh, Sprecher, and Whelan (20, 22, 70, 72, 74) studied the solvolysis reactions of compounds XIIa, XIIIa, XIVa, and XVa. It was



found (22) that XIIa and XIIIa reacted with aqueous silver nitrate in 4 hr. at room temperature to give the corresponding alcohols. XIVa reacted in 4 hr. with silver nitrate in aqueous dioxane at 65°C. to give a quantitative yield of silver bromide. The corresponding alcohol (XIVb) was isolated in 40 per cent yield (40). A quantitative yield of silver bromide was also obtained from XIVa with silver nitrate in 70 per cent ethanol after 2 hr. at 65°C.

Ethanolysis (22) of XIIIa was first order in XIIIa and independent of ethoxide-ion concentration, demonstrating that the reaction is not a frontside S_N2 displacement. The solvolysis constant of XIIa at 100°C. in 70 per cent aqueous dioxane was $0.68 \times 10^{-6} \text{ sec.}^{-1}$, compared with 0.82 sec.^{-1} for *tert*-butyl bromide at 100°C. in 80 per cent aqueous alcohol, a result which emphasizes the fact that though the bicyclo[2.2.2]octyl halides are more reactive than any previously mentioned bridgehead halides, they are still extraordinarily unreactive for tertiary halides.

Other reactions of these systems which may be presumed to involve carbonium-ion intermediates are the conversions of 1-hydroxy- and 1-bromobicyclo[2.2.2]octanes (XIIb and XIIa) to 1-chlorobicyclo[2.2.2]octane with zinc chloride and concentrated hydrochloric acid, and the conversion of XIIb to XIIa with zinc bromide and concentrated hydrobromic acid (70). XIIIb was converted to XIIIa by means of 48 per cent hydrobromic acid at 100°C. (72), providing another

example of a carbonium-ion reaction and confirming the structure of XIIIb, which was obtained in the solvolysis of XIIIa in ethanol.

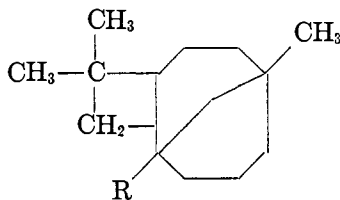
7. 1-Bromobicyclo[2.2.1]heptane

By contrast with the fairly high reactivity observed in the preceding substances, 1-bromobicyclo[2.2.1]heptane (XVa) gave no appreciable reaction with aqueous ethanolic silver nitrate at 100°C. for 1 hr. (74), but did react with aqueous silver nitrate at 150°C. giving, in 2 days, a considerable amount of silver bromide and of 1-hydroxybicyclo[2.2.1]heptane (XVb) (22). It was felt that the difference in reactivity between XIIa and XVa could be considered strong evidence that a tetrahedral (sp^3) configuration of the carbonium ion is of considerably higher energy than a planar (sp^2) configuration. It was noted that XIIa and XVa do not differ appreciably in the importance of the other factors thought to stabilize carbonium ions: namely, hyperconjugation (neglecting any possibility for steric inhibition of such conjugation), solvation, relief of B-strain, resonance, and inductive effect. Using more recent data, the strain energy for the formation of a planar bicyclo[2.2.2]octyl cation (VIII) was estimated to be just 6 kcal. (22), in contrast with the older estimate of 22.5 kcal. Details of the calculation were not given, however, and the value seems too low, particularly in view of the recent value of 26 kcal. (35a) for the strain energy of cyclobutane.

The foregoing relative order of stability of the bicyclo[2.2.1]heptyl and bicyclo[2.2.2]octyl cations was confirmed by Franklin and Field, who found that the appearance potentials of the carbonium ions in the gas phase are 10.66 e.v. and 9.98 e.v., respectively (27a).

8. Large bridged rings

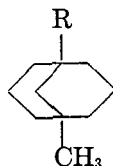
The chemistry of bridgehead halides in larger ring systems has not been explored thoroughly, but there are indications that in the larger ring systems, where a planar configuration about the bridgehead would produce relatively little strain, carbonium-ion reactions proceed with ease (12). Thus, β -caryophyllene alcohol (XVIa) reacts with phosphorus pentachloride to give the corresponding chloride (XVIb) (73), which with sodium acetate and acetic acid



- XVIa: R = OH
 XVIb: R = Cl
 XVIc: R = OCOCH₃

yields the acetate (XVIc) (32). A bromide and an iodide were similarly prepared (73). The chloride, however, failed to react measurably with concentrated sodium ethoxide in 12 hr. at 100°C. (32). Compound XVIIa is likewise converted

easily to the chloride XVIIb with phosphorus pentachloride (55). S_N2 displacement and elimination are still prevented in this system, however, as indicated by the fact that XVIIb showed no reaction with boiling dimethylaniline. In contrast with the ease of conversion of XVIa and XVIIa to the corresponding



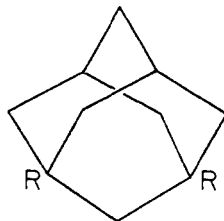
XVIIa: R = OH

XVIIb: R = Cl

chlorides, 1-apocamphanol (VIb) yielded only a sulfite containing no halogen when treated with thionyl chloride (8), a reaction for which there is evidence for a carbonium ion-pair as intermediate (15). With phosphorus pentachloride (8) VIb gave only a molecular compound with hydrogen chloride (after the reaction mixture was poured into water).

9. The von Braun reaction

The contrast between small and large bridged rings is further illustrated by the von Braun reaction of phosphorus pentahalides with *N*-substituted amides, in which a carbonium ion or ion-pair is a likely intermediate (39). Whereas the dibenzamide of diaminoadamantane (XVIIIa) was readily converted to di-



XVIIIa: R = C₆H₅ CONH

XVIIIb: R = Br

XVIIIc: R = CONH₂

XVIIId: R = COOH

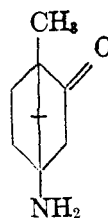
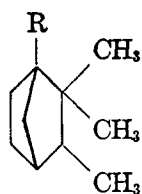
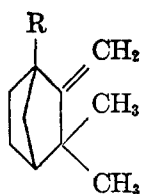
XVIIIe: R = H

bromoadamantane (XVIIIb) by means of phosphorus pentabromide (52), the benzamide of 1-aminoapocamphane (VIc) gave only starting materials and tars when treated with phosphorus pentachloride (8).

10. The reaction of primary amines with nitrous acid and nitrosyl chloride

The reaction of primary amines with nitrous acid is commonly thought to go by way of carbonium-ion intermediates (68), but at bridgehead carbons, where the reaction goes with ease, it has been suggested without experimental confirmation (8) that some other path, such as a concerted S_Ni mechanism (1c), might be involved. The following amines have been converted to the corresponding bridgehead alcohols by treatment with nitrous acid: 1-aminoapocamphane

(VIId) (8); 1-aminocamphene (XIXa) (27, 43); 4-aminodihydrocamphene (XXa) (33); 4-aminocamphor (XXI) (33); apotricylylamine (XXII) (44); XXIII (3);

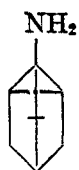


XIXa: R = NH₂
 XIXb: R = H
 XIXc: R = Cl
 XIXd: R = CON₃

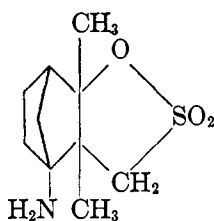
XXa: R = NH₂
 XXb: R = H
 XXc: R = CONH₂

XXI

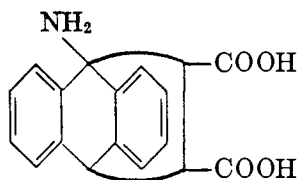
XXIV (6); and 1-aminobicyclo[2.2.1]heptane (XVc) (74). A carbonium-ion



XXII

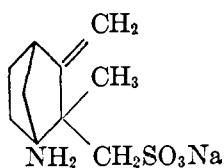


XXIII

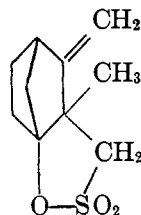


XXIV

mechanism rather than an *S_Ni* mechanism seems strongly indicated by the conversion of XXV to XXVI with nitrous acid (3). A reaction similar to that of the amine with nitrous acid is the conversion of 1-aminoapocamphane (VIId) to 1-chloroapocamphane (VIa) with nitrosyl chloride in ether (8).



XXV



XXVI

11. The hydride-chloride exchange reaction

An attempt to prepare 1-chlorobicyclo[2.2.1]heptane (XVe) by the aluminum chloride-catalyzed exchange with *tert*-butyl chloride yielded only norbornyl chloride (XXXII) (71). This was explained by Schmerling as due to instability of the expected bridgehead carbonium ion, but may be also regarded as only

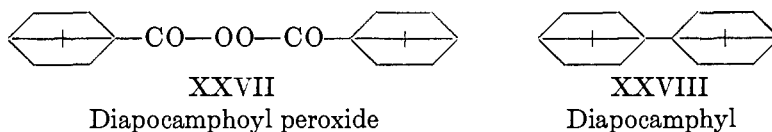
another demonstration of the abnormally high stabilities of norbornyl cations as compared with ordinary secondary cations (67).

B. BRIDGEHEAD FREE RADICALS

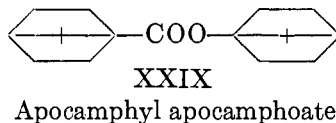
Except in cases where steric inhibition of resonance is involved, bridgehead radical reactions seem to proceed without particular difficulty, although bridgehead hydrogens seem to be somewhat less prone to free-radical attack than would be expected from their tertiary character.

1. Diapocamphoyl peroxide decomposition

Decomposition of diapocamphoyl peroxide (XXVII) in carbon tetrachloride solution was found (36) to give a complex mixture of products, including



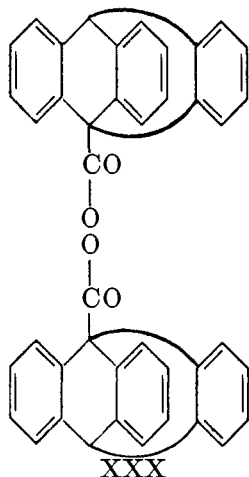
1-chloroapocamphane (VIa), 36 per cent; diapocamphyl (XXVIII), 9 per cent; apocamphoic acid (VIe), 5 per cent; apocamphyl apocamphoate (XXIX), 50 per cent; and hexachloroethane. A mechanism involving free apocamphyl radicals was proposed to explain the products. Although it was suggested by



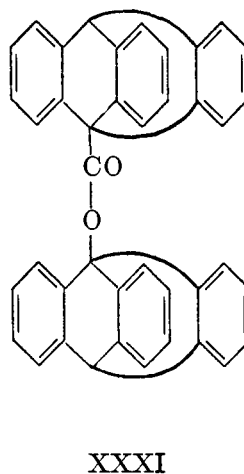
Sager (69) that the products could be formed by bimolecular collisions of carboxylate radicals, Bartlett and Lewis (9) pointed out that there were no analogies for a frontside displacement by carbon tetrachloride to give VIa as observed. The reaction may be regarded as the most convincing case on record for the occurrence of a true hydrocarbon free radical in the decomposition of an acyl peroxide.

2. Ditrptooyl peroxide decomposition

The similar decomposition of ditrptooyl peroxide (XXX) in benzene was found to give a similar mixture of products (7), including triptycene (Vc), 45 per cent; 1-triptycyl triptoate (XXXI), 6 per cent; 1-hydroxytriptycene (Vd), 17 per cent; triptoic acid (Ve), 31-38 per cent; 1,1'-ditrptooyl (?), 1-2 per cent; and biphenyl. The major part of the products were explained by a mechanism involving free triptycyl radicals. The rates of this reaction and of the diapocamphoyl peroxide decomposition in benzene (69) were such as to indicate very little difference in ease of formation of the bridgehead radicals and the methyl radical (from diacetyl peroxide), but the extra stabilization ordinarily present in tertiary radicals as compared with methyl seemed to be absent. The isolation of triptycene and biphenyl indicated that the triptycyl radical was more reactive



Ditriptyoyl peroxide

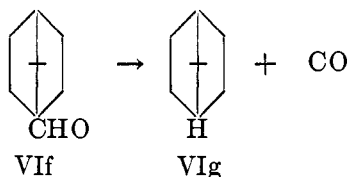


1-Triptycyl triptoate

than the phenyl radical. In the presence of iodine, 1-iodotriptycene (Vb) was formed instead of triptycene.

3. Decarbonmonoxylation

The decarbonmonoxylation reaction, believed to involve free-radical intermediates (76), has been found to go smoothly in one bridgehead case. Apocamphane-1-carboxaldehyde (VI_f) was converted to apocamphane (VI_g) on refluxing with *tert*-butyl peroxide (21). From this it was concluded that the bridgehead radical is not of prohibitively high energy.

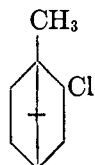


4. Attempted bridgehead chlorinations

However, attempts to effect bridgehead chlorination on bicyclo[2.2.1]heptane (XV_d) (67) and triptycene (V_c) (10) have not been successful, the former giving mainly norbornyl chloride (XXXII) and the latter giving no reaction. Triptycene also failed to react with chlorine in carbon tetrachloride during several days' exposure to ultraviolet light (10). Bornyl chloride (XXXIII) was the first



Norbornyl chloride



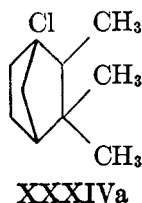
Bornyl chloride



2,3-Dichlorocamphane

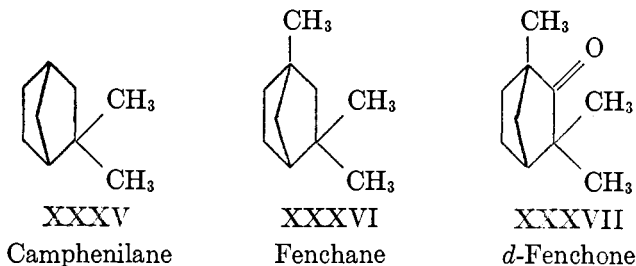
product obtained by the chlorination of camphane in chloroform in sunlight (28). Further chlorination in carbon tetrachloride with sunlight gave a mixture from which only 2,3-dichlorocamphane (XXXIV) was isolated.

Apparently the only case in which chlorination has been reported to occur at a bridgehead is in the chlorination of isocamphane (XXb) in petroleum ether with sunlight (29). However, the structure assigned to the product, XXXIVa, seems inconsistent with the ease of dehydrohalogenation using aniline (25a).

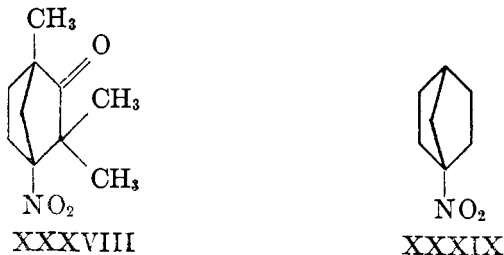


5. Bridgehead nitration

Nitration with dilute nitric acid at 140°C. of camphane (IXc), camphenilane (XXXV), isocamphane (XXb), and fenchane (XXXVI) gave no tertiary nitro compounds (46, 47).



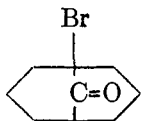
By contrast, however, *d*-fenchone (XXXVII) reacted with dilute nitric acid at 130°C. to give good yields of a tertiary nitro compound, believed to be XXXVIII (38, 48-50). Vapor-phase nitration of bicyclo[2.2.1]heptane at 400°C. gave a 50 per cent yield of a tertiary nitro compound, presumably XXXIX (13).



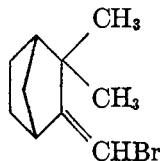
6. Brominative decarboxylation of silver salts

The brominative decarboxylation of silver salts, believed to involve free-radical intermediates (16), has been employed successfully in the preparation

of a number of bridgehead bromides, including XIa (64), dibromoadamantane (XVIIIb) (52), 1-bromoapocamphane (VIh) (75), XL (19), 4-bromocamphane



XL



XLI

8-Bromocamphene

(IXb) (40), 1-bromobicyclo[2.2.1]heptane (XVa) (74), and 1-bromobicyclo[2.2.2]octane (XIIa) (70). The yields are usually 50–60 per cent. When the preparation of VIh was carried out in carbon tetrachloride (75), large amounts of 1-chloroapocamphane (VIa) accompanied the desired product, strongly suggesting an intermediate free radical.

7. Attempted allylic bromination at bridgeheads

One of the possible mechanisms for allylic bromination of olefins with *N*-bromosuccinimide involves an intermediate allylic radical obtained by removing an allylic hydrogen atom. Partly to test this mechanism, the reaction of *N*-bromosuccinimide with camphene (XXb) was investigated (65). The only allylic hydrogen in this compound is at a bridgehead, and the resonance stabilization of the intermediate radical would therefore be sterically inhibited (*cf.* Bredt's rule (25d)). The products were 8-bromocamphene (XLI) and more reactive monobromides, but nothing that could be identified as a bridgehead bromide. Similarly, norbornylene (XLII) reacted with *N*-bromosuccinimide to give 27–40 per cent yields of 3-bromonorbornylene (XLIII), but no bridgehead bromide (66).



XLII

Norbornylene



XLIII

3-Bromonorbornylene

8. Reactions of bridgehead halides with metals

Attempts to generate free radicals from 1-bromotriptycene (Va) by heating with silver in dry mineral oil at 280°C. or by heating with copper powder or zinc dust were not successful (9). Va reacted slowly with sodium in hot mineral oil or with magnesium in ether, but carbonation led only to triptycene (Vc), indicating a very reactive intermediate anion or radical which removed hydrogen from the solvent. Compound IV also failed to react with silver powder in boiling acetone or xylene (6). An attempt to prepare a Grignard reagent from 1-chloroapocamphane under ordinary conditions failed (8).

9. Catalytic reduction of bridgehead halides

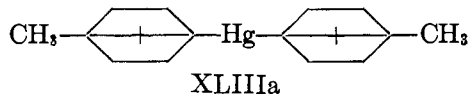
Catalytic reductions of bridgehead halides with Raney nickel have been carried out in a number of cases without particular difficulty. The reaction mechanism is uncertain, but is classified here as a radical reaction by analogy with the corresponding reduction of dialkyl sulfides, for which there is some evidence for free-radical intermediates (14). The compounds which have been reduced to the corresponding hydrocarbons are dibromoadamantane (XVIIIb) (52), XVIIb (55), 1-bromo-3,3-dimethylbicyclo[2.2.2]octane (XIIIa) (40, 72), 1-bromobicyclo[2.2.2]octane (XIIa) (70), and XIa (64).

10. Kolbe electrolysis of apocamphoic acid

Dauben and Muhs (19a) found that Kolbe electrolysis of apocamphoic acid (VIe) in methanol gave 1-methoxyapocamphane (VIj), 32 per cent; apocamphyl apocamphoate (XXIX), 10 per cent; diapocamphyl (XXVIII), 33 per cent; and recovered VIe, 9.4 per cent. The reaction was slow and inefficient. This fact, together with the unusually high yields of methyl ether (VIj) and Simonini ester (XXIX) and the low yield of coupling product (XXVIII), suggested a particularly reactive apocamphyl radical as intermediate.

11. Sodium stannite reduction of bridgehead mercury compound

Winstein and Traylor (72a, 77) reduced 4-camphylmercuric chloride (IXe) to di-4-camphylmercury (XLIIIa) by treatment with sodium stannite.



A free-radical intermediate is considered probable because the analogous reduction of *trans*-2-methoxycyclohexylmercuric iodide with sodium stannite and cleavage of the resulting dialkylmercury with mercuric chloride (a stereospecific *S_Ni* reaction) gives a mixture of *cis*- and *trans*-2-methoxycyclohexylmercuric chlorides.

12. Reaction of bridgehead mercury compound with iodine

4-Camphylmercuric iodide (IXf) reacts with iodine in dioxane to give 4-iodocamphane (IXg) in 88 per cent yield (72a, 77). The free-radical character of this type of reaction is indicated by its inhibition by oxygen, by the irregularity of reaction rates, by sensitivity to light and peroxides, and by lack of dependence of the rate on the concentration of the mercurial (35b, 72a, 77).

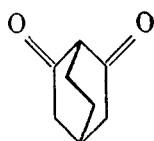
C. BRIDGEHEAD ANIONS AND ENOLS

Data on bridgehead anions are less plentiful than for cations and radicals, but the early indications are that the anions may be formed without unusual difficulty except where steric inhibition of resonance is involved.

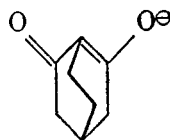
1. Anions involving inhibition of resonance and bridgehead enols

(a) 2,6-Diketobicyclo[2.2.2]octane

2,6-Diketobicyclo[2.2.2]octane (XLIV) was found to have none of the usual enolic properties associated with 1,3-diketones (11). It gave no color with ferric



XLIV



XLIVa

chloride and had no greater solubility in alkali than in water. The enolate ion, XLIVa, formed by removal of the bridgehead proton would violate Bredt's rule (25c) in the same manner as the camphenyl radical previously discussed (page 1078). The failure of XLIV to react with alkali gives no information about the general stereochemical requirements of carbanions not stabilized by conjugation with neighboring groups.

(b) 1-Bromobicyclo[3.3.1]nonan-9-one

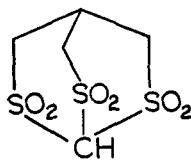
Compound XL similarly failed to react with bromine in acetic acid, a result which was explained as due to instability of the intermediate enol according to Bredt's rule (18).

(c) Triptycyl anion

Triptycyl anion formation is sterically inhibited in the same manner as the cation (page 1068) and the radical (page 1075). Thus triptycene (Vc) gives no exchange with phenylisopropylpotassium under conditions (21 hr. in ether) which give immediate reaction in the case of triphenylmethane (10). Likewise, it was not found possible to decarboxylate triptoic acid (Ve) by heating the sodium salt with soda lime at 350°C. or by refluxing the acid in quinoline containing copper chromite (7).

(d) Bicyclic trisulfone

By contrast, the bicyclic sulfone XLV has a very acidic bridgehead hydrogen, being soluble in aqueous bicarbonate (23). It is uncertain whether the acidity is due to a large inductive effect, removing charge from the bridgehead, or whether



XLV

the geometry of the anion might be such that resonance stabilization is not inhibited.

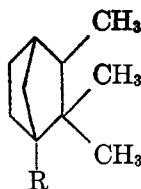
(e) Decarboxylation of β -keto acids

The decarboxylation of β -keto acids in which the carboxyl group is at a bridgehead provides another example of steric inhibition of resonance, since the intermediate enolate ion or enol must have a double bond or a partial double bond at the bridgehead. The expected correlation between ring size and ease of decarboxylation is hence observed. These reactions have been reviewed previously (25b).

2. Anions not involving resonance inhibition

(a) Bridgehead alkali metal derivatives

The most clear-cut bridgehead anions known are probably the organometallic derivatives, of which a number have been prepared recently. Doering and Schoenewaldt (24) succeeded in preparing a metallic derivative of 4-chlorodihydrocamphene (XLVIa) (mixture of stereoisomers) by treatment with sodium-potassium alloy in pentane. Carbonation yielded a mixture of the corresponding bridgehead acids (XLVIb). More recently it has been found convenient to



XLVIa: R = Cl
XLVIb: R = COOH

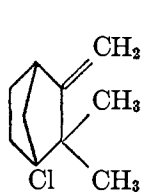
employ lithium sand in cyclohexane. By this method the following halides have been converted to the corresponding carboxylic acids: 4-chlorocamphane (IXa) (40), 4-bromocamphane (IXb) (40), 1-chlorobicyclo[2.2.1]heptane (XVe) (74), 1-bromobicyclo[2.2.1]heptane (XVa) (74), and 1-chlorobicyclo[2.2.2]octane (XIIc) (70). The yields were usually 50-70 per cent.

4-Camphyllithium has also been converted to 4-iodocamphane (IXg), 4-bromocamphane (IXb), and 4-camphylmercuric chloride (IXe) by treatment with iodine, bromine, and mercuric chloride, respectively (72a, 77).

(b) Sodium and alcohol reduction of bridgehead halides

The reduction of bridgehead halides with sodium and alcohol proceeds with ease. A carbanion intermediate seems reasonable (72), but it has been pointed out that a radical intermediate is also a possibility if the radicals are sufficiently reactive to react exclusively with the solvent rather than with each other (since no dimer is obtained in these cases) (30). The halides which have been reduced to the corresponding hydrocarbons by this method are 4-chlorocamphane (IXa) (24), 1-chlorocamphene (XIXc) (35, 45), 4-chlorocamphene (XLVII) (35, 45),

2,4-dichlorocamphane (XLVIII) (35, 45), 4-chlorotricyclene (XLIX) (35, 45), XIIIa (40, 72), XIVa (40), and 1-chlorobicyclo[2.2.1]heptane (XVe) (74).



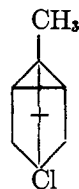
XLVII

4-Chlorocamphene



XLVIII

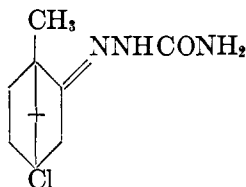
2,4-Dichlorocamphane



XLIX

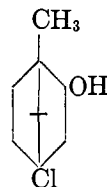
4-Chlorotricyclene

Likewise, 4-chlorocamphor semicarbazone (L) was reduced to camphor semicarbazone (34), 4-chloroisoborneol (LI) was reduced to isoborneol (35), and IV



L

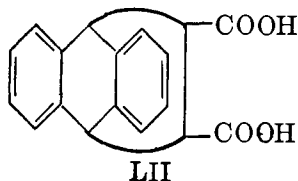
4-Chlorocamphor semicarbazone



LI

4-Chloroisoborneol

gave a small yield of the diacid LII (6).



LII

(c) Lithium aluminum hydride reduction of bridgehead mercury compound

A reaction most probably involving a free carbanion as intermediate is the reduction of 4-camphylmercuric chloride (IXe) to camphane (IXc) with lithium aluminum hydride, carried out in 19 per cent yield by Winstein and Traylor (72a, 77).

D. THEORETICAL EXPECTATIONS REGARDING STABILITIES OF BRIDGEHEAD INTERMEDIATES

The foregoing data on bridgehead cations, radicals, and anions are, at least, not in disagreement with quantum-mechanical expectations. Carbonium ions are predicted to be most stable in the planar configurations (37, 42), in excellent agreement with the experimental results with bridgehead derivatives.

Quantum-mechanical predictions of the configurations of radicals and anions

are more ambiguous. Both planar and pyramidal configurations have been derived for carbon radicals by different workers (31a, 42). The expected configuration of the anion seems also uncertain (31b), although a pyramidal configuration has been predicted for the methyl anion (42). Ammonia, which is isoelectronic with the methyl anion, is well known to be pyramidal.

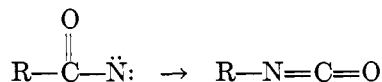
Bridgehead reactions involving radicals and anions tend to proceed with greater ease than carbonium-ion reactions, in agreement with hypotheses of preferred pyramidal configurations of radicals and anions. However, the data do not permit any final conclusion as yet in this regard. Comparative data for large and small bridged-ring systems are not yet available for radical and anion reactions.

III. CONCERTED DISPLACEMENT REACTIONS

Reactions included in this section are those in which the displacing atom is believed to participate in the removal of the departing atom, so that no intermediate cation, radical, or anion is involved.

A. INTRAMOLECULAR DISPLACEMENTS

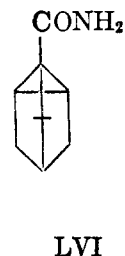
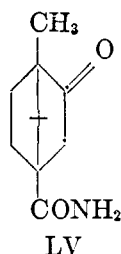
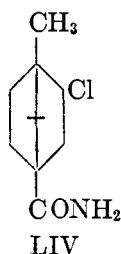
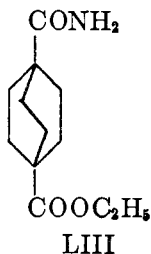
The bridgehead displacements which are known to go by concerted intramolecular or cyclic mechanisms are mostly of the type involving movement of the bridged-ring system from carbon to an electron-deficient nitrogen atom. These include the Hofmann, Curtius, and Schmidt reactions (1a).



All of these reactions proceed with no apparent difficulty at bridgehead carbons.

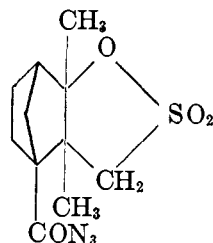
1. Hofmann reaction

The Hofmann reaction has been used to convert the following amides to the corresponding amines: XVIIIc (52), VII (8), LIII (64), XXc (33), LIV (33), LV (33), and LVI (44).



2. Curtius reaction

The Curtius reaction has been employed to convert the following acid azides to the corresponding isocyanates: triptolic acid azide (Vf) (7), LVII (2), and camphene-1-carboxylic acid azide (XIXd) (2).



LVII

3. Schmidt reaction

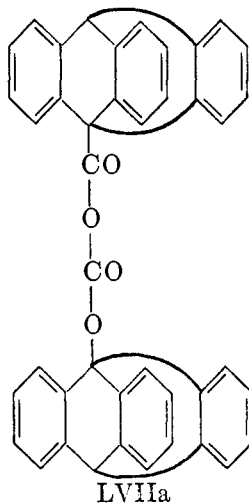
By means of the Schmidt reaction, camphane-4-carboxylic acid (IXd) (40) and bicyclo[2.2.1]heptane-1-carboxylic acid (XVf) (74) were converted to the corresponding amines.

4. Reaction of primary amines with nitrous acid

The reactions of bridgehead primary amines with nitrous acid, which might possibly involve concerted intramolecular displacements, have been discussed under carbonium-ion reactions (page 1073).

5. Rearrangement of ditriptyoyl peroxide

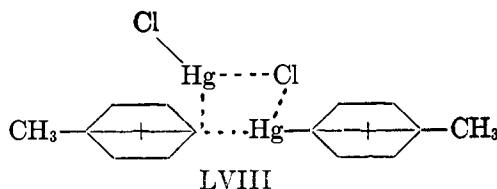
A possible migration of a triptycyl group to an electron-deficient oxygen was postulated to explain the appearance of a second crop of triptoic acid (Ve) in the decomposition of ditriptyoyl peroxide (XXX) (page 1075) (7, 30). It was proposed that part of the peroxide might have rearranged to LVIIa, which then hydrolyzed during the isolation procedure to give more triptoic acid.



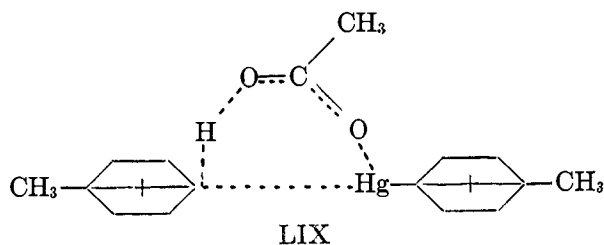
6. Displacements involving bridgehead mercurials

Winstein and Traylor (72a, 77) have found three cases of displacement of bridgehead mercury atoms which very likely proceed through cyclic (S_{Si}) mechanisms.

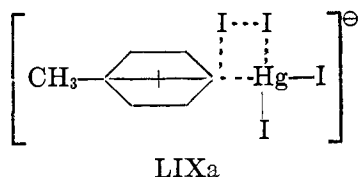
Di-4-camphylmercury (XLIIIa) reacts with mercuric chloride in ether at room temperature to give an 86.5 per cent yield of 4-camphylmercuric chloride (IXe).



XLIIIa solvolyzes in acetic acid to give camphane (IXc, not isolated) and 4-camphylmercuric acetate. Evidence for a cyclic mechanism in this reaction was found in other systems (35b, 72a, 77).



4-Camphylmercuric iodide (IXf) reacts with triiodide ion in aqueous dioxane to give 4-iodocamphane (IXg). The kinetics are first order in the mercurial and first order in the triiodide.



All of these reactions are fast, the rates where measured being comparable to those of open-chain compounds. The transition states for the reactions might be pictured respectively as LVIII, LIX, and LIXa.

B. BIMOLECULAR DISPLACEMENTS

1. Nucleophilic displacements

Bimolecular nucleophilic displacements apparently occur only with Walden inversion (1b) and are therefore not possible at bridgeheads. Thus, apocamphyl *p*-toluenesulfonate (LX) (8) gave no reaction in 23 hr. refluxing with lithium iodide in acetone, and even the α -bromoketone XL (18) showed no reaction with sodium iodide in acetone. Ethanolysis of XIIIa (22) was independent of ethoxide-ion concentration. The chloride (XVIb) from β -caryophyllene alcohol did not

react with quinoline at 210°C. in 3 hr. or with refluxing sodium ethoxide in 12 hr. (32).

2. Radical displacements

Concerted bimolecular radical displacements on carbon are apparently rare. None seem to have been sought or found at bridgeheads.

3. Electrophilic displacements

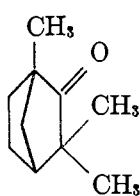
Winstein and Traylor (72a, 77) found that di-4-camphylmercury (XLIIIa) solvolyzes in acetic acid (page 1085) at a greatly enhanced rate if perchloric acid is added. Rough second-order kinetics were observed, first order in the mercurial and first order in the acid. It is believed that this can be accounted for only by a direct S_N2 displacement at the bridgehead, with a hydrogen ion displacing a 4-camphylmercuric ion. The reaction is offered as evidence that second-order electrophilic substitution (S_E2) normally proceeds with retention of configuration, by contrast with the inversion invariably resulting from S_N2 displacements.

IV. MISCELLANEOUS DISPLACEMENT REACTIONS

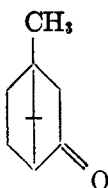
A few bridgehead displacements have been observed about whose mechanisms little or nothing is known. It does not appear profitable to speculate on the mechanisms here.

A. BIOLOGICAL OXIDATIONS AT BRIDGEHEAD POSITIONS

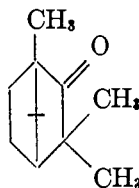
Several bridged-ring compounds have been fed to dogs and isolated from the urine as glucuronides of tertiary alcohols, presumably formed by bridgehead oxidation. Compounds which have undergone this conversion include fenchone (LXI) (60, 62, 63), epicamphor (LXII) (59), 3,3-dimethylcamphor (LXIII)



LXI
Fenchone

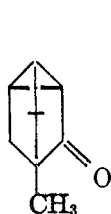


LXII
Epicamphor

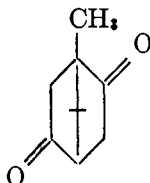


LXIII
3,3-Dimethylcamphor

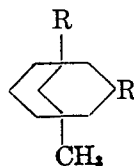
(58), cyclocamphanone (LXIV) (61), and *p*-diketocamphane (LXV) (61).



LXIV
Cyclocamphanone



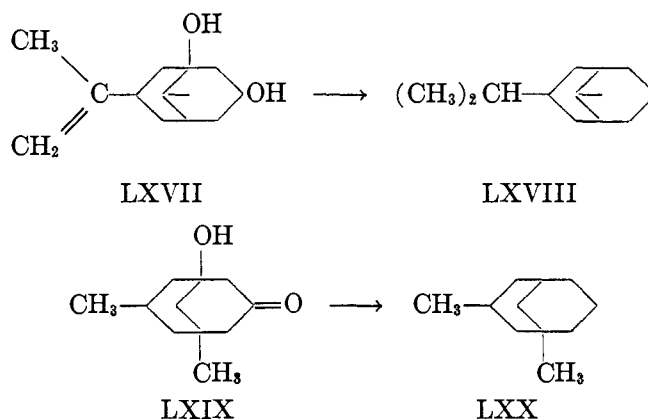
LXV
p-Diketocamphane



LXVIa: R = OH
LXVIb: R = H

B. REDUCTION OF ALCOHOLS WITH PHOSPHORUS AND HYDRIODIC ACID

The reduction of alcohols to hydrocarbons with phosphorus and hydriodic acid at 195–250°C. has been used to convert LXVIIa to LXVIII (54), LXVII to LXVIII (57), and LXIX to LXX (56).



C. REDUCTION OF A BRIDGEHEAD HALIDE WITH ZINC AND HYDROCHLORIC ACID

The bromoketone XL was reduced to bicyclo[3.3.1]nonane with zinc amalgam and hydrochloric acid under Clemmensen reduction conditions (19).

D. PYROLYTIC DECARBOXYLATION USING COPPER BRONZE

Adamantanedicarboxylic acid (XVIIIId) was decarboxylated in 2.4 per cent yield to give adamantane (XVIIIe) by heating with copper bronze at 400°C. (51).

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