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The Stereochemistry Of Halogenation, Dehalogenation And Related Reactions Of Camphor

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THE STEREOCHEMISTRY OF HALOGENATION, DEHALOGENATION AND RELATED REACTIONS OF CAMPHOR

by

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ABSTRACT

The stereochemistry of halogenation and dehalogenation of derivatives of camphor, a ketone incapable of conformational change, has been studied.

The halogenation of 3-halocamphors under a variety of conditions resulted in the preferential entry of the entering halogen from the endo direction by a factor of 1.5 compared to 1 for exo. These reactions are believed to involve the enol of halocamphors. Halogenation of the enol acetates of 3-halocamphors showed endo preference to the extent of 4-99 against 1 for exo entry of the halogenating agent. The sodium and lithium enolates on the other hand exhibited a preference for exo entry of the entering halogen to the extent of over 1.5 compared to 1 for endo entry. Thus, the preference for endo entry of halogen decreases in the order enol ester, enol and enolate.

The halogenation of camphor itself has been studied under kinetically controlled conditions. While the enol and enolate of camphor show a clear preference for exo entry of the halogen, the enol acetate of camphor gives product resulting from preferential endo entry.

These results were rationalised by advancing a view that the halogenation of these intermediates (the enol, enol ester or enolate) is under the control of two competing effects. The first of these

effects is termed "steric" and seems to have its origin in the steric interactions between C-8 methyl group, the C-3 substituent and the entering electrophile, which disfavour exo entry of the reagent. The second effect is termed "stereoelectronic" and favours exo entry. The origins of the "stereoelectronic" effect, which seems to be inherent in the bornane skeleton, have been suggested by other workers to be torsional interactions involving the bridgehead substituents.

It was not possible to separate the two epimeric 3-bromo-3-chlorocamphors, resulting from the halogenation of 3-halocamphors, by physical means. These epimers have been prepared in a high degree of purity by means of stereoselective synthesis and their properties studied. In the reductive dehalogenation by triphenylphosphine in aqueous acetonitrile the 3-exo-bromo-3-endo-chlorocamphor debrominates four times faster than the other epimer. Since this dehalogenation is presumed to approach the condition of being the microscopic reverse of the halogenation reaction, the selectivity in debromination from two orientations can be rationalised as effects of the torsional factor. A number of other dehalogenating agents showed lower selectivity in exo-debromination.

It has also been confirmed more quantitatively that the enolate of camphor shows a high degree of selectivity in deuteration from exo side and that in the enolisation of camphor the C-3 exo proton is removed preferentially.

All of these results can be rationalised on a consistent basis, viz. the operation of steric and torsional factors.

ACKNOWLEDGMENTS

Foremost I should like to express my sincere gratitude to my guide and mentor, Prof. Edgar Warnhoff, for suggesting the problem and for encouragement and guidance at all stages of the project.

My thanks are also due to various members of the faculty as well as my colleagues for being helpful in numerous ways. In particular the assistance rendered by Prof. J.B. Stothers in carrying out P.M.R. decoupling experiments is highly appreciated.

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INTRODUCTION

A. GENERAL

It has been established that the halogenation of ketones proceeds through an enol or enolate ion as an intermediate, involving catalysis by acids* in the former and bases in the latter case.**[1,2] Studies on acid or base catalysed halogenation of ketones, as well as halogenation of enol ethers and enol esters of ketones have revealed two broad types of directional influences. These are classified as (a) stereoelectronic factors and (b) steric factors, which may either oppose each other or reinforce each other.[3,4,5]

In cyclohexanone derivatives, stereoelectronic factors favour that transition state which allows maximum continuous overlap of p-orbitals in the halogenation.[3d] This is the energetically favoured path in the removal of an α-proton to form an enol or enolate, as well as in the formation of products (α-haloketones) from these intermediates. In the chair form of cyclohexanones (where both the starting material and the products are in the chair form) such as in Fig. 1., the axial proton Ha should be removed preferentially for the reasons of better orbital overlap. Similarly in the halogenation of enol, enolate, enol ethers or enol esters

*An enol can also be an intermediate in base catalysed halogenation in a proton donating medium.

**Recent work indicates that this reaction may be more complex than it has been assumed to be so far.

the transition state tends towards chair (or boat) so as to make the reagent assume an axial-like orientation in order to have maximum possible p- overlap.[3-6] This statement assumes that the transition states resemble the ketone.

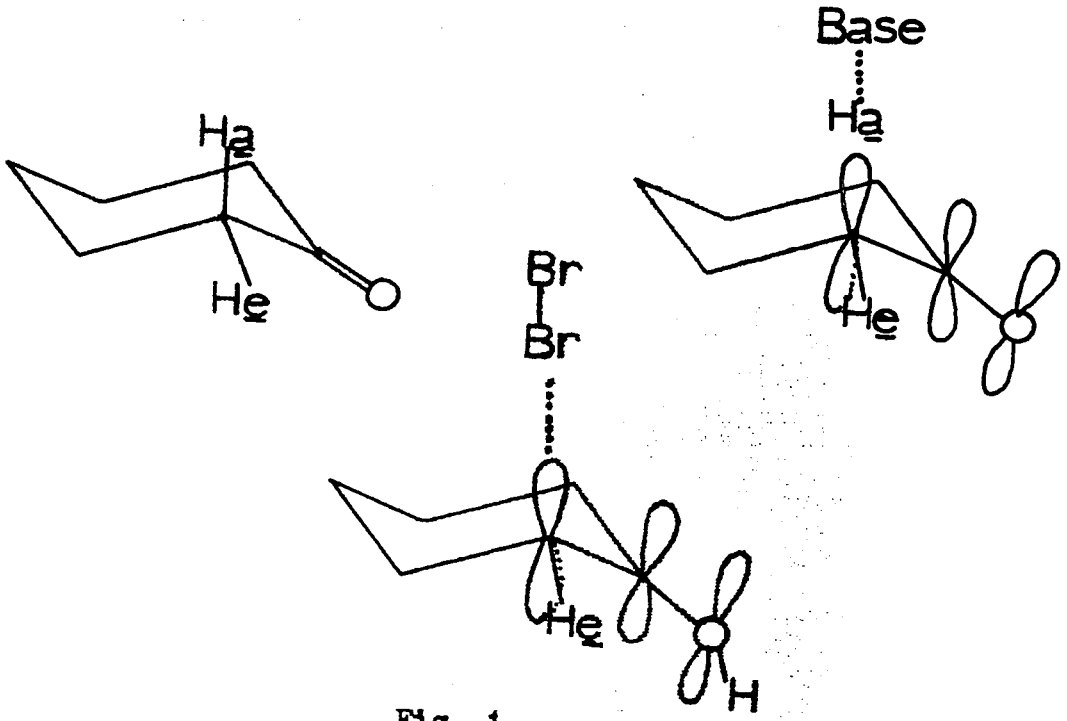


Fig. 1.

On the other hand the intermediate in proton removal or halogenation of ketones, viz. an enolate or enol is planar as in Fig.2., with no distinction between axial and equatorial orientation. If the

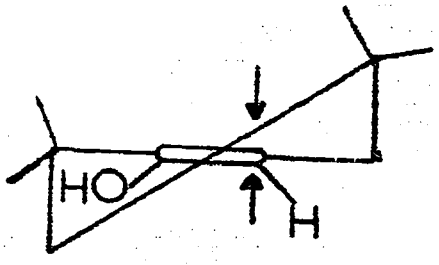


Fig. 2.

transition states do resemble this planar intermediate there should be no distinction in the p -orbital overlap from either side indicated by arrows in Fig. 2.

These two models of transition states, Fig. 1. and Fig. 2., are therefore two extremes. The actual transition states would probably be intermediate between these two extremes, with varying degrees of likeness either to Fig. 1 or to Fig. 2 depending on the system.

The steric factor might hinder the axial approach of base in proton removal or axial approach of reagent in halogenation due to severe 1,3-interactions. In conformationally mobile cyclohexanones these interactions might force enolisation and bromination to proceed through a boat like transition state, as in Fig. 3. A 4,4-dialkyl substituted cyclohexanone for example would offer severe hindrance to axial approach of base, or axial approach of bromine (if the transition state is ketone like). Similar hindrance would also be experienced with substituents at the 6 position shown in Fig. 4.

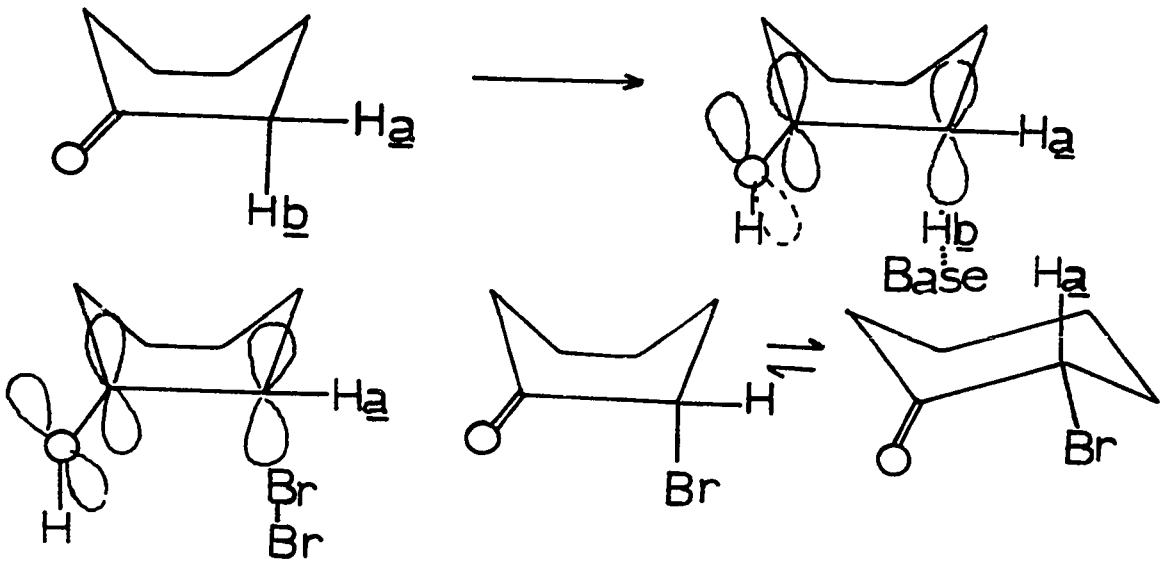


Fig. 3.

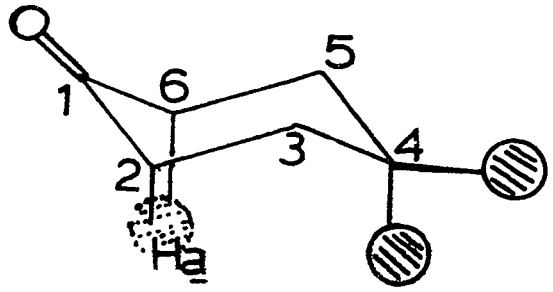


Fig. 4.

A "boat-axial" entry of reagent gives a "boat-axial" haloketone which in mobile systems results in equatorial disposition of the substituent after conversion to the chair conformation. 1,3-Diaxial interaction between bromine and a substituent larger than hydrogen is probably sufficient to cause reactions to occur *via* the boat-like transition state leading to an equatorial bromoketone in conformationally "fixed" systems.[7-12] Another category of steric effects which affect the course of proton removal from and halogenation of ketones may be termed "conformational" influences. A representative case of conformational influences is the "reflex effect".* Substituents which do not directly interact in the normal steric sense, being remote from the site of the reaction, can none the less distort the geometry of the ketone and perhaps the transition state.

However, products of halogenation of ketones quite often do not parallel the predictions made on the basis of the foregoing steric and stereoelectronic considerations. The usual conditions of halogenation lead to the formation of hydrogen halide as a side product, which is capable of either enolising the first formed haloketone, or epimerising it by a dehalogenation-

* See ref. 45, page 127.

rehalogenation route, leading to the thermodynamically more stable epimer (usually a mixture)[3a-d,7-9,12-14] as shown in Fig. 5. Ample proof for both epimerisation mechanisms exists.[12]

Methods are available to remove the hydrogen halide from the reaction mixture in order to trap the kinetically controlled

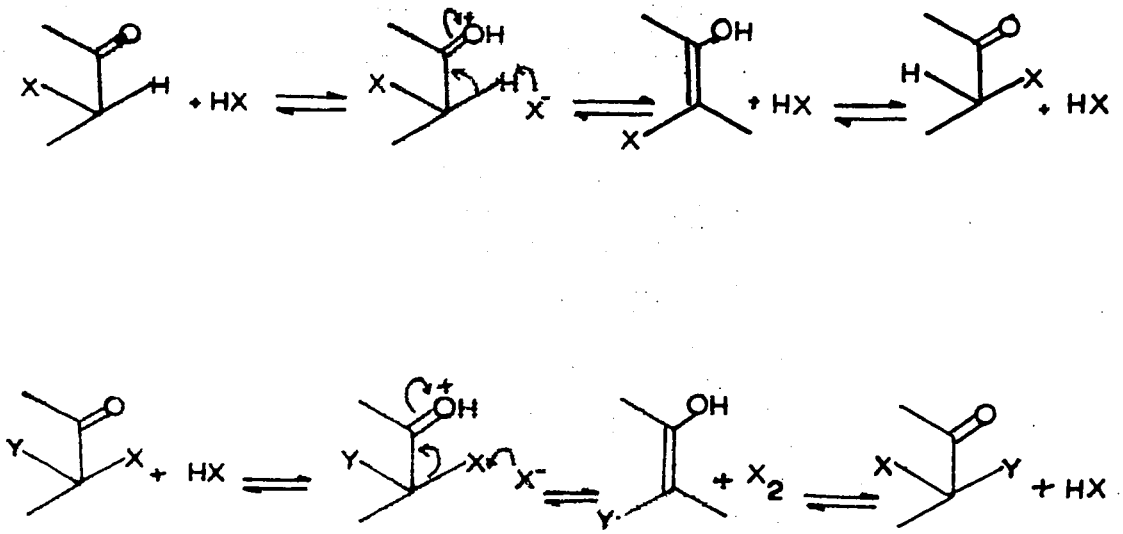


Fig. 5.

product. Some of these procedures are (a) use of excess sodium acetate in glacial acetic acid[7-14], (b) use of pyridine hydrobromide perbromide in glacial acetic acid[15], (c) use of potassium chlorate[16], etc. Use of these methods has made it possible to obtain more precise information regarding the directional control in the halogenation of cyclohexanone derivatives and the results seem to conform to the predictions based on the concept of the steric and stereoelectronic control in the halogenation of ketones.

The factors which influence thermodynamic stability of one or the other epimeric α-haloketone have their origin in electronic

and steric interactions in the α-haloketones, viz. in interactions between the halogen substituent and the carbonyl group and between the halogen substituent and other substituents that may either interact with the α-halogen sterically or conformationally. In cyclohexanones the steric factors arise principally from 1,3-diaxial interactions. In the chair form of an α-halocyclohexanone the interactions are small between the axial halogen (product from "kinetic control") and the 4- or 6- axial proton. These become significant when the 6- or 4- axial substituent is larger than hydrogen.

Electronic factors are generally of the nature of dipole-dipole interactions between the carbonyl oxygen and α-halogen. From electrostatic consideration[3a] of the dipole vectors it has been suggested that the interactions would be severe when the α-carbon halogen bond is in the same plane as the σ -plane of the carbonyl group and would be minimized when the former is at right angles with the latter (Fig. 6).

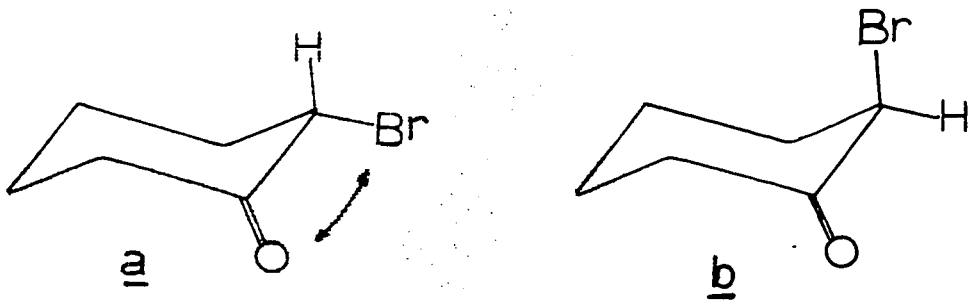


Fig. 6.

This type of interaction is reflected in the infrared stretching frequency of carbonyl group in form 6a which is usually 20 ~ 30 cm^{-1} higher than that of the unsubstituted ketone[17]. Corey concluded that in unsubstituted α-bromocyclohexanone form 6b (bromine

axial) will be >97% at room temperature. Recent studies by Stothers, et al.[18] show that the preference for axial bromoepimer is 80-90%.

Similar studies on either the "frozen"[19] boat form of cyclohexanones or on cyclopentanones are limited. Amongst easily accessible ketones which could serve as a model to investigate steric and stereoelectronic effects in either a "frozen" boat cyclohexanone with ring strain, or in a "rigid envelope" cyclopentanone, camphor deserves attention. The merits of this particular molecule are its ready availability in a high degree of optical purity, ease of handling, and the enormous amount of information available on the properties of the parent ketone itself as well as its derivatives.

A survey of pertinent information already available on the halogenation of camphor now follows:

B. HALOGENATION OF CAMPHOR. A HISTORICAL REVIEW.

Interest in camphor chemistry[20] dates back to the late nineteenth century when even the bicyclic nature of the compound was not fully understood. Surprisingly detailed and at times fairly accurate information was obtained on the course of halogenation of this compound, information which has stood the test of time. We will use the numbering system here which is currently accepted in the chemical literature. For the sake of brevity the correct generic name (1,7,7-trimethyl bicyclo(2,2,1)heptan-2-one) or its synonym (bornan-2-one) will not be used; the parent ketone will be called camphor and its derivatives will also be

written accordingly. Table I summarises the current terminology used in this dissertation and gives the equivalent used in the old literature.

The absolute configuration of D(+)-camphor used here is the one determined by Allen and Rogers[21] for (+)3-endo-bromo-D-camphor by the anomalous dispersion X-ray technique, and refers to 3-(+)bromo-D-camphor of the old literature with melting point 75°-76°, $[\alpha]_D$ +135° (ethanol). The three dimensional formula is shown in fig. 7. The absolute configuration of this molecule as obtained by X-ray methods is in accord with those obtained by optical rotatory dispersion studies.

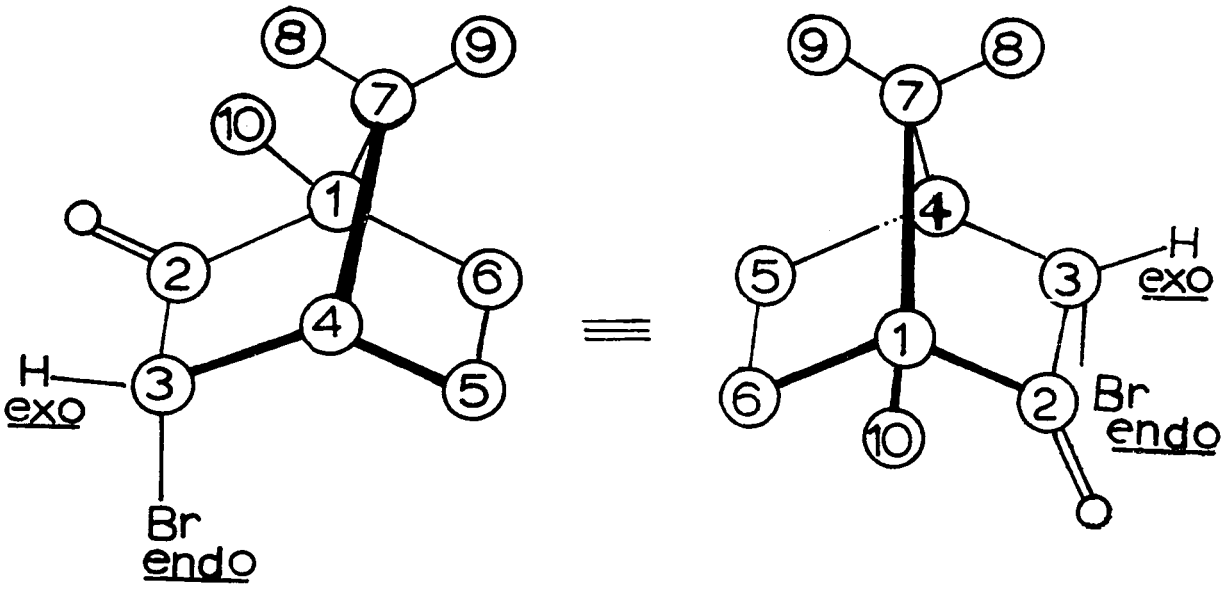


Fig. 7.

(+)3-endo-Bromo-D-Camphor.
White circles are carbon atoms and are numbered. Where there is no substituent, hydrogen atoms are implied.

Table I

Old Nomenclature	Current Nomenclature
α-Substituents eg. α-Bromocamphor	3-endo eg. 3 endo-Bromocamphor
α'-Substituents eg. α'-Chlorocamphor	3-exo eg. 3 exo-Chlorocamphor
ω-Substituents eg. Camphor-ω-Sulfonic acid (also called β - by mistake) in older literature.	Substituents on Carbon 10, eg. Camphor-10-Sulfonic acid
π-Substituents eg. π-Bromocamphor (also called 8-bromocamphor)	Substituents on Carbon 9, eg. 9-Bromocamphor (all derivatives in the so-called 8 - position when anti to carbonyl group are substituents on carbon-9: only those derivatives which are known to be syn to the carbonyl group on the bridge methyl are to be called 8)

Direct monobromination[22-28] of camphor gave a mixture of epimeric 3-bromocamphors. Marsh[24] first isolated a product from this mixture, after making it alkaline, which crystallised readily from ethanol, had a melting point of 76° and $[\alpha]_D$ + 135° (alcohol) when prepared from D(+)-camphor. This is now known to be the 3-endo-bromo-D-camphor epimer. From the direct monobromination mixture of D(+)-camphor Marsh[28] isolated another 3-monobromocamphor with $[\alpha]_D$ + 29.4° (ethanol, minimum figure). This was not a pure compound as judged from its non-crystalline nature. By a tedious fractional crystallisation procedure Lowry and Steele[29] later isolated a product, melting point 78° after nine crystallisations, $[\alpha]_{5461}$ - 40° (ethanol) which they con-

cluded to be the other epimer of 3-monobromocamphor (ie. 3-exo-bromo-D-camphor) of unknown purity.

Armstrong[23] in 1878 and Kipping in 1905[30] had shown that the epimeric 3-monobromocamphors undergo a base-catalysed epimerisation forming a mixture of two epimers. Lowry[29] investigated this mutarotation and obtained the same equilibrium mixture of epimers starting from the form with high positive specific rotation (3-endo-bromo-D-camphor) and the form with low negative specific rotation (3-exo-bromo-D-camphor). Using partial solubility data and optical rotations Lowry found that the equilibrium mixture had 92% of 3-endo-bromo-epimer and 8% of 3-exo-bromo-epimer around room temperature in ethanol. Therefore, from the relationship $\Delta F = -2.303\ RT \log K = 1.44$ kcal/mole, 3-endo-bromo-D-camphor is more stable by 1.44 kcal/mole compared to 3-exo-bromo-D-camphor at room temperature in ethanol solution.

Direct chlorination of camphor[22b-c,31-36] has been carried out in solvents by molecular chlorine, or by the action of sulfuryl chloride on camphor in sealed tubes at elevated temperatures. The mixture obtained from direct chlorination contains both epimers of 3-monochlorocamphor. On making this mixture alkaline one of the epimers crystallises out from ethanol. Repeated crystallisations to constant melting point gave the product with melting point 94°, $[\alpha]_D$ + 96.2° (ethanol) now known to be 3-endo-chloro-D-camphor. In 1915 Lowry[35] isolated 3-exo-chloro-D-camphor, melting point 117°, $[\alpha]_D$ + 35° (ethanol). Lowry also observed base-catalysed epimerisation of the epimeric 3-chlorocamphors and obtained the same epimeric mix-

ture starting from either of the two epimeric monochlorocamphors. The equilibrium concentration of 3-endo-chloro-D-camphor in ethanol was 91% and that of 3-exo-chloro-D-camphor was 9%. Calculation gives $\Delta F = -1.427$ kcal/mole in favour of the 3-endo epimer at room temperature in ethanol.

Judging from the specific rotations of the direct monochlorination product of D-(+) camphor Lowry[36] concluded that the first formed chlorination products contain more of the exo-epimer than present in the equilibrium mixture.

The epimeric composition of 3-halocamphors was done under conditions which gave products from thermodynamic control. However, no information is available on the proportions of epimeric monohalocamphors on halogenation under conditions known to be "kinetically controlled." Information on this point is difficult to seek for two reasons: (1) base catalysed (acetate buffered) halogenation of camphor is a very slow process[37] and is not amenable to precise studies, and (2) the monohalocamphors are very susceptible to epimerisation by bases and to a lesser extent by strong mineral acids.

In 1898 Lowry[36] published the results of his studies on the course of halogenation of camphor. In agreement with Marsh[24,28] he noted that the first isolated product from either chlorination or bromination of camphor consisted of a mixture of readily interconvertible epimeric 3-monohalocamphors. Due to limitations of techniques at that time he decided to study the halogenation of monohalocamphors since the epimeric 3-bromo-3-chlorocamphors thus formed are less prone to epimerisation under the conditions

he used. He anticipated that chlorination of 3-monobromocamphor and bromination of 3-monochlorocamphor would lead to two 3-bromo-3-chlorocamphors.

By treating 3-endo-chloro-D-camphor with bromine on a water bath, and after two crystallisations from ethanol a mixture of epimeric 3-bromo-3-chlorocamphors was obtained with melting point 53°-55°, $[\alpha]_D^{19°}$ + 51°(c=10, chloroform). After twenty-six recrystallisations from six different solvents a fraction was obtained with melting point 61°, $[\alpha]_D^{20°}$ +16° (c=10, chloroform). The mother liquors from the first few fractionations yielded a 3-bromo-3-chlorocamphor epimeric mixture, with melting point 55°, $[\alpha]_D^{20°}$ +63.9° (c=7.02, chloroform) in less than 5% of the total yield of epimeric 3-bromo-3-chlorocamphors. In a later study he obtained identical results from the bromination of 3-exo-chloro-D-camphor also[35] (Apparently epimeric 3-bromo-3-chlorocamphors, probably isomorphous, crystallise in a series of crystal forms with different proportions of the two epimers).

Direct chlorination of 3-monobromocamphor was more difficult. When 3-endo-bromo-D-camphor was heated with one mole equivalent of sulfuryl chloride in a sealed tube at 130° for six hours, the product after two recrystallisations from methanol had a melting point of 56°, $[\alpha]_D$ + 25.7° (chloroform).

Twenty-six recrystallisations from six different solvents gave a fraction, melting point 61°, $[\alpha]_D^{20°}$ + 10.3°(c=10, chloroform).

Lowry[36] was convinced that he had separated at least one of the epimeric 3-bromo-3-chlorocamphors in pure form. Physical

constants for this form, which gave no change in specific rotation and melting point on successive recrystallisations, are: melting point 61°, $[\alpha]_D^{20°}$ + 10° (C = 10, chloroform). Lowry considered the fact that the two epimeric monochlorocamphors have smaller magnitudes of specific rotation (3-endo-chloro-D-camphor, $[\alpha]_D$ + 95°, 3-exo-chloro-D-camphor, $[\alpha]_D$ + 35° in ethanol) compared to the magnitudes of the specific rotation of 3-monobromocamphors (3-endo-bromo-D-camphor $[\alpha]_D$ = 135°, 3-exo-bromo-D-camphor $[\alpha]_{5461}$ - 40°,in ethanol), and he argued that in the 3-bromo-3-chlorocamphors the orientation of the bromine substituent will be the controlling factor in the observed magnitude of specific rotation. On this basis he assigns the epimer (according to him a pure compound) which had $[\alpha]_D$ + 10° (C = 10, chloroform), the same orientation of bromine as in 3-exo-bromo-D-camphor, $[\alpha]_{5461}$ - 40° (ethanol). This epimer should therefore be termed 3-exo-bromo-3-endo-chloro-D-camphor. The other epimer for which he gave a specific rotation figure higher than +65° is therefore 3-endo-bromo-3-exo-chloro-D-camphor.

Reaction of both epimers with alcoholic potassium hydroxide resulted in debromination and the organic product after recrystallisation was 3-endo-chloro-D-camphor. Similarly reaction with zinc in acetic acid also resulted in debromination, the product after recrystallisation was identified as 3-endo-chloro-D-camphor.

From his results Lowry inferred that the intermediate in the halogenation of the 3-monohalocamphors must be their

enol,* since both 3-monochlorocamphor on bromination and 3-monobromocamphor on chlorination afforded a mixture of 3-bromo-3-chlorocamphor epimers. Moreover, bromination of 3-exo-chlorocamphor afforded the same mixture of 3-bromo-3-chlorocamphors (judged by specific rotation) as was obtained from 3-endo-chlorocamphor under identical conditions.[35]

In the light of subsequent work on the steric and stereoelectronic factors governing the course of halogenation of ketones the following comments can be made on Lowry's work.

1. Lowry undertook his studies at a time when the structure of the camphor molecule itself was not settled. With the present understanding of severe steric requirements of this molecule a reassessment of the stereochemistry assigned to epimeric 3-bromo-3-chlorocamphors by independent physical means is necessary.

2. The epimeric mixture of chlorobromocamphors which Lowry examined was obtained under what are now understood to be "equilibrating conditions". Although he has shown that hydrochloric acid in acetic acid does not significantly alter the epimer composition at 100°C, it is possible that this particular epimer mixture, $[\alpha]_D^{20°}$ + 48.8° (chloroform) might fortuitously be the equilibrium mixture and would therefore show no change in epimer composition. If so, it is desirable to check this result for the two epimers separately, or if they are not pure at least show that the epimer composition is not altered for two different epimer compositions.

* The contemporary idea of "enol" intermediate in the halogenation of ketones was due to Lapworth.[1]

3. The methods of analysis used by Lowry involved recrystallisation to separate the products from starting materials. Since recrystallisation steps do lead to some fractionation they alter the product composition in as much as the distribution of epimeric halocamphors (whether mono- or dihalo derivatives) is not the same in the mother liquor and in the crystals. Lowry's conclusions regarding the direction of halogen entry are based on specific rotation figures on materials which have been recrystallised twice. These figures therefore may not be representative of the true epimeric ratio in the first formed product.

4. Polarimetric methods of analysis have their limitations in that they are reliable only when the rotation data for all the components in the mixture are known precisely. Even so the method becomes useless if more than two optically active components are present.

5. At the time Lowry undertook his studies he had no way of knowing whether his compounds were pure.

6. Lowry's results do not give any information on the relative stabilities of epimeric 3-bromo-3-chlorocamphors. Whether or not the two epimers do equilibrate under the conditions of halogenation this information is still very important in elucidating the course of halogenation of camphor.

In concluding the general Introduction an outline of the aims and objectives of the present enquiry is given below:

C. AIMS AND OBJECTIVES OF PRESENT RESEARCH

The primary aim of this investigation was to elucidate the steric and stereoelectronic factors which operate in the halo-

genation and related reactions of camphor. With this end in view it was desired

(1) to develop methods for accurate and unambiguous identification and estimation of various products that may be envisaged, or shown to form, on halogenation of camphor.

(2) To reexamine the halogenation of 3-monochloro and 3-monobromocamphors under the conditions described by Lowry, without recourse to crystallisations and quantitatively estimate the ratio of epimeric 3-bromo-3-chlorocamphors.

(3) To attempt to carry out halogenation of 3-monochloro- and monobromocamphors under conditions which would give products from kinetic control, and estimate the ratio of first formed epimeric 3-bromo-3-chlorocamphors.

(4) To prepare pure epimeric 3-bromo-3-chlorocamphors, characterise them and obtain data about their stabilities by suitable methods, both qualitative and quantitative, available at present. This includes studies on the course of dehalogenation of epimeric 3-bromo-3-chlorocamphors.

(5) To obtain similar information on the course of monohalogenation of camphor and if possible its enol derivatives.

(6) To obtain information on the steric and stereoelectronic course of enolisation of camphor, and of protonation of the enolate or enol of camphor.

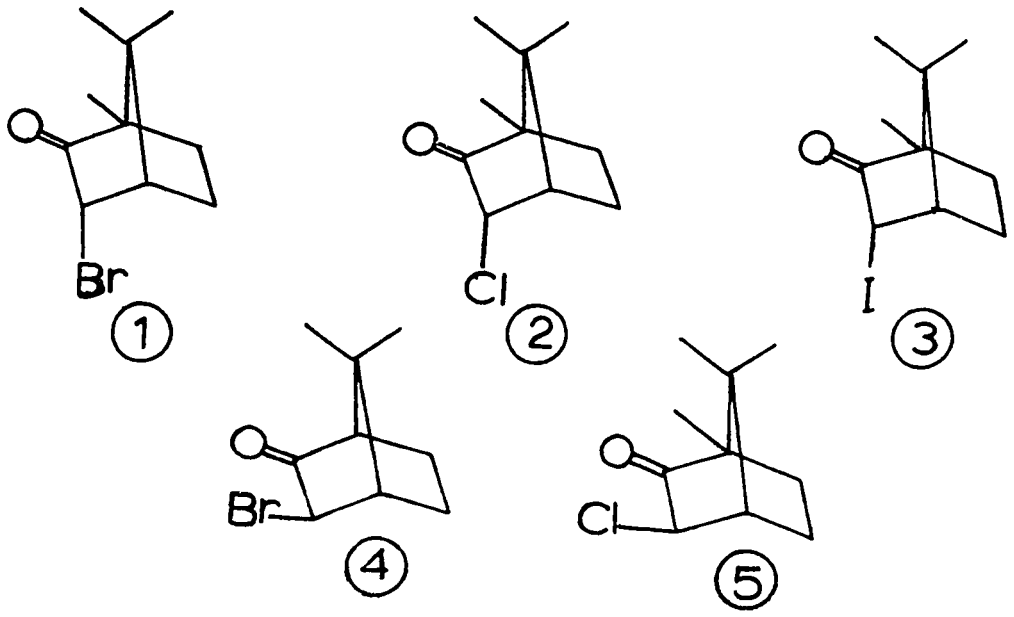
(7) To correlate the information obtained from objectives (2)-(6) with the steric and torsional factors that are known to operate in the camphor molecule.

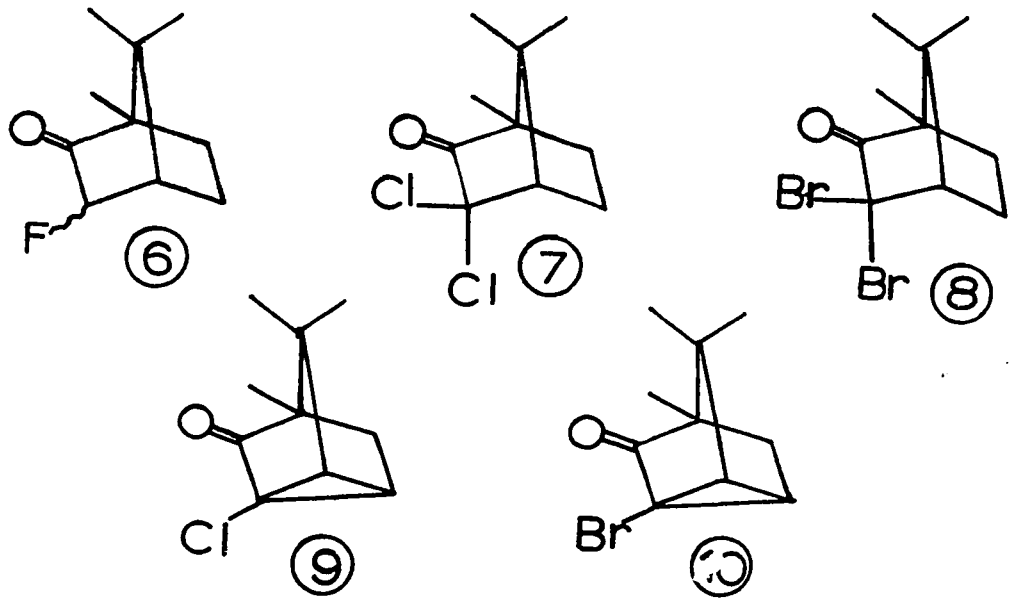
II

3-HALOGEN DERIVATIVES OF CAMPHOR

A. INTRODUCTION

3-Halogen derivatives of camphor are well known compounds and their physical properties have been documented in section I.B. Of particular interest in the study of the steric and stereoelectronic course of the halogenation and dehalogenation of camphor derivatives are methods which not only distinguish these derivatives but also allow assignment of stereochemistry unequivocally. As reference compounds in the exploration of suitable methods, the following derivatives of D(+)-camphor were prepared:





Compounds (4) and (5) contained ~ 30% of the endo epimers. Compound (6) was a mixture of two epimers in about equal amounts.

Standard literature procedures were used to prepare the 3-halo derivatives, with such modifications as are indicated in the Experimental section. Compound (3) (3-endo-iodo D-camphor) was prepared by iodinolysis of 3-acetoxymercuri-D-camphor which became accessible by direct acetoxymercuration of D-camphor enol acetate. Difficulties were encountered in preparing 3,3-dichloro camphor following the published procedures. In later experiments this compound was prepared by iodine-catalysed chlorination of 3-chloro-D-camphor enol acetate by a solution of chlorine in carbon tetrachloride at room temperature. Compounds (9) and (10) have been prepared for the first time. Their inclusion in this list is discussed in relation to the infrared spectra of camphor derivatives.

B. PHYSICAL CHARACTERISTICS OF 3-HALOCAMPHORS

Some of the useful information available on the physical properties of the above mentioned derivatives is discussed below:

1. X-Ray Diffraction:

X-ray diffraction measurements have been reported for 3-endo-chlorocamphor, 3-endo-bromocamphor and 3-endo-cyanocamphor by Wiebenga and Crom[38]; for 3-endo-bromocamphor by Northolt and Palm[39] and by Allen and Rogers.[21]

The bond lengths and angles for 3-endo-bromo-D-camphor taken from the published data of Allen and Rogers[21] are shown below:

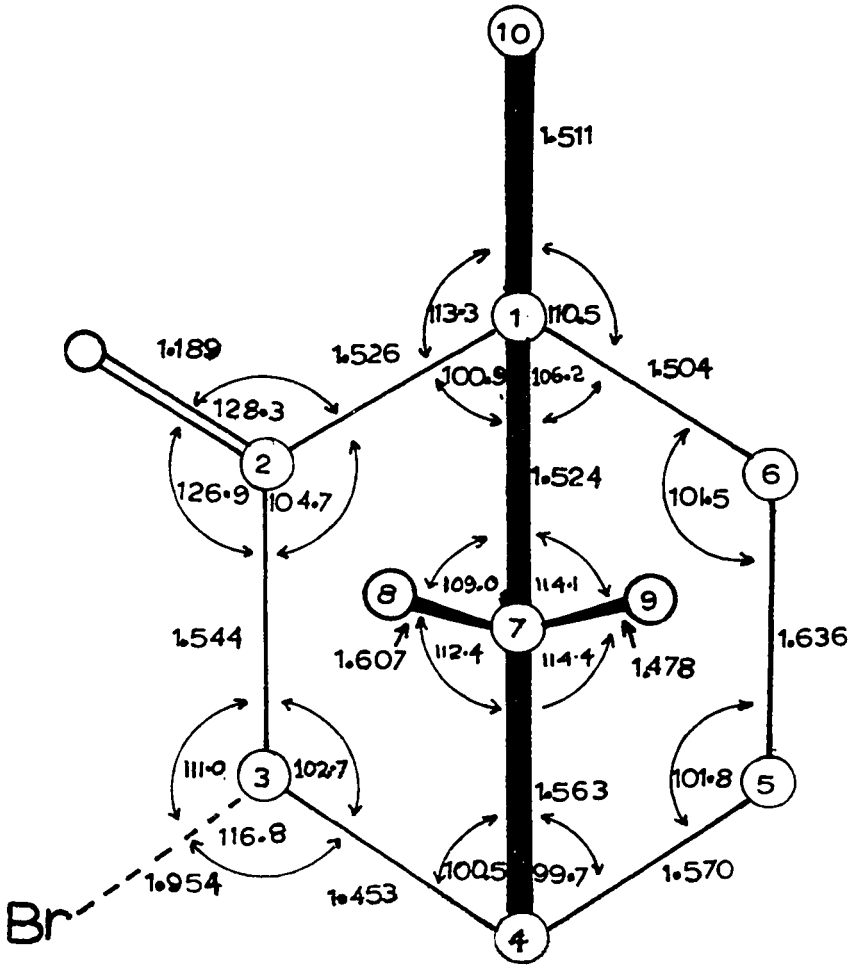


Fig. 8.

2. Dipole Moments:

A comparative study of the dipole moments of 3-mono- and 3,3-dihalocamphors was undertaken by Kumler, et al.[40] The dipole moments of 3-endo-chlorocamphor and 3-exo-chlorocamphor are identical within the experimental error in three different solvents (hexane, benzene and dioxane). The authors concluded that the angle between the σ-plane of the carbonyl group and the C_3-X bond axis must be identical in the exo and endo dispositions of X. Such a disposition of C_3 substituents in relation to the carbonyl plane is termed "bisectional". This method is not likely to be useful in stereochemical assignments to halocamphors.

3. Infrared Spectra.

Table II summarises the infrared characteristics of the reference compounds and lists the carbonyl stretching frequencies of 3-halocamphors along with the values reported by Brutcher, et al.[41] for comparison. The carbonyl stretching frequencies of α-haloketones had been shown by Jones, et al.[17] to be shifted in comparison with that of the unsubstituted ketone depending on the angle between the σ-plane of the carbonyl group and the α-C-X bond. In the chair form of α-halo cyclohexanones the shift in carbonyl stretching frequency, $\Delta\nu = \pm 3$ cm^{-1} when the halogen occupies axial position but is between 8-27 cm^{-1} (depending on the halogen) in the equatorial disposition of the halogen atom[3]. The $\Delta\nu$ values are $\sim$27 cm^{-1} for chlorine, 15-22 cm^{-1} for bromine and $\sim$8 cm^{-1} for iodine[42]. It will be observed from the table II that the $\Delta\nu$ for 3,3-dihalocamphors is nearly twice that for the

monohalocamphor. Moreover the $\Delta\nu$ values for 3-endo-chlorocamphor and 3-exo-chlorocamphor are almost identical. Brutcher, et al.[41] concluded from their observations that the halogen substituent in camphor is in bisectional position i.e. the angle between the C-X bond and the C_2-C_3 bond in camphor molecule is exactly half of the tetrahedral angle.

It is interesting to note that the $\Delta\nu$ for 3-halo-3,5-cyclocamphanones (entries 9 and 10, Table II) are almost twice that for 3 - monohalocamphors, and are in good agreement with the value for equatorial α-halocyclohexanones.

4. Optical Rotation:

Lowry used this criterion extensively in checking the purity of his products as well as in his investigations in the stereochemistry of halogenation of camphor. Table III lists our values for the specific rotations of 3-halocamphors. All these derivatives were prepared from the same lot of D(+) camphor, $[\alpha]_D^{20^\circ}$ = +41.4° (c = 8.2, chloroform). Contributions to the molecular rotation by the halogen substituent at C_3 position are calculated and shown as $[M]_D Y$ values in Table IV. These values can be used to calculate the molecular rotations of epimeric 3-bromo-3-chlorocamphors by the approximation of optical superimposition as illustrated in section VE. This method is useful in the characterisation of pure compounds but is severely limited as an analytical tool in the present investigations.

5. Ultraviolet Absorption

Absorption due to the $n \rightarrow \pi^*$ transition of the carbonyl group in camphor occurs in the 290mμ region. The effect of

TABLE II

INFRARED CHARACTERISTICS OF 3-HALOCAMPHORS AND 3,5-CYCLO-D-CAMPHANONE

No.	Compound	(a) $\nu_{C=O}^{CS_2}$ max cm.$^{-1}$	(a) $\Delta\nu$ cm.$^{-1}$	(b) $\nu_{C=O}^{CCl_4}$ max cm.$^{-1}$	(b) $\Delta\nu$ cm.$^{-1}$
1	D(+) Camphor	1743		1744	
2	3-endo-Chlorocamphor	1758	15	1763	19
3	3-endo-Bromocamphor	1755	12	1758	14
4	3-endo-Iodocamphor	1753	10		
5	3,3-Dichlorocamphor	1773	30	1774	30
6	3,3-Dibromocamphor	1763	20	1766	22
7	3-exo-Chlorocamphor			1762	18
8	3,5-cyclo-D-Camphanone	1752			
9	3-Chloro-3,5-cyclo-D-camphanone	1780	28		
10	3-Bromo-3,5-cyclo-D-camphanone	1779	27		

(a) Present work, KBr cells

(b) Reference 41.

α-halogen substituents on this absorption band is of interest in relation to the orientation of the substituent in an α-haloketone. Cookson[43] found that the $n \rightarrow \pi^*$ transition of α-halocarbonyl compounds shifts to a longer wavelength (lower energy) compared to the unsubstituted carbonyl compound when the α-halogen is axial with a concomitant increase in the molar extinction coefficient; this effect is small in magnitude and opposite (shift to smaller wavelengths) or is negligible when the halogen occupies the equatorial position. Cookson (loc. cit.) has correlated these red shifts with the angle θ defined by the projection of the carbonyl-oxygen double bond and α-carbon halogen bond viewed from down the axis of C_1-C_2 bond. Theoretical explanation for the relation between the orientation of the α-halogen in the α-haloketone and the ultraviolet absorption characteristics of α-haloketone in comparison with the unsubstituted ketone has been provided by Corey[3] and Kosower, et al.[44], and more recently by Eliel, et al.[45] and by Allinger, et al.[46] Cookson[43] has also examined the ultraviolet absorption of 3-halocamphors. In 3-endo-bromocamphor the $n \rightarrow \pi^*$ transition band of the carbonyl group is shifted towards longer wavelengths, the shift in the absorption maximum compared to camphor, expressed as $\Delta\lambda = +16.5$ mμ, with a related increase in the extinction coefficient, $\Delta \log \epsilon = +0.5$. The solvent effect on this red shift on going from ethanol to cyclohexane is negligible. The extent of the red shift in 3,3-dibromocamphor is +35 mμ, almost twice that caused by 3-endo bromine substituent. It can thus be seen that both endo as well as exo halogen substituents at C-3 position in camphor cause

a red shift of identical magnitude. The relative position of the halogen substituent with regard to the sigma plane of carbonyl group is thus identical in both these orientations, an observation which is in line with the bisectional bond conclusion derived from dipole moment[40] and infrared studies.[41]

This method, like infrared, is not of much value in the camphor series.

6. Optical Rotatory Dispersion and Circular Dichroism

Djerassi, et al.[47] extended the earlier measurements of Lowry and coworkers[48] in the shorter wavelength region of the ultraviolet. D(+) camphor as well as the α-halogenated derivatives of D(+) camphor have a positive Cotton effect curve. Dispersion peaks for 3-endo-chloro-D-camphor and 3-exo-chloro-D-camphor occur at the same wavelength; the peaks for 3,3-dichloro-D-camphor have moved to longer wavelengths, with related increase in amplitude. The dispersion peaks of 3-endo-bromo- and 3,3-dibromo-D-camphor behave likewise. This method also falls short of the requirements as an analytical tool in the study of halocamphors.

C. Conclusion

In evaluating the available physical methods for identification and estimation of 3-halocamphors, none of the physical methods discussed in the present section, except optical rotation are of much value. As an analytical method optical rotation too is completely useless for mixtures containing more than two components. Preliminary information available on the proton magnetic resonance (P.M.R.) spectra of 3-halocamphors indicated that

TABLE III

OPTICAL ROTATIONS OF 3-HALO-D-CAMPHORS

COMPOUND	$[\alpha]_D^{CHCl_3}$	$[M]_D$
D (+) Camphor	+41.4° (20°, c = 8.2)	+63°
3-<u>endo</u>-Chloro-D camphor	+95.5° (20°, c = 8.59)	+178°
3-<u>endo</u>-Bromo-D-camphor	+135.3° (19°, c = 8.59)	+313°
3-<u>endo</u>-Iodo-D-camphor	+168.8° (19.5°, c = 3.34)	+470°
3,3-Dichloro-D-camphor	+58.9° (20°, c = 8.1)	+130°
3,3-Dibromo-D-camphor	+39.8° (19°, c = 8.16)	+123°

TABLE IV

CONTRIBUTION TO MOLECULAR ROTATION OF D(+)CAMPHOR

BY C-3 SUBSTITUENT, Y.

Y	NOTATION	$[M]_D Y$
endo Chlorine	$[M]_D$ NCl	+ 115
exo Chlorine	$[M]_D$ XCl	- 48
endo Bromine	$[M]_D$ NBr	+ 250
exo Bromine	$[M]_D$ XBr	- 190
endo Iodine	$[M]_D$ NI	+ 407

this was potentially a very useful method. A detailed examination of this method follows in section III.

III

PROTON MAGNETIC RESONANCE SPECTRA OF CAMPHOR AND 3-HALOCAMPHORS

A. Previous Work:

Kumler, Schoolery and Brutcher[49] published the P.M.R. spectra of 3-halogenated camphors at 40 Mc. They recognised two regions of interest in these spectra viz. (1) a low field single proton signal around 3.9 - 5.1 p.p.m. appearing in the spectra of 3-mono-halogenated camphors and (2) a methyl region around 1 p.p.m. common to camphor and all of its 3-substituted derivatives.

The 3.9 - 5.1 p.p.m. signal was assigned to the 3-methine proton. In 3-endo-halocamphors this appeared as a doublet with J = 5-6 c.p.s. The splitting was ascribed to the coupling between 3-exo methine proton (halogen endo) and the C-4 proton (bridge-head hydrogen). In the 3-exo-haloepimers the signal from the 3-endo methine proton was a singlet, appearing $\sim$0.5 p.p.m. upfield, compared to the 3-exo methine proton signal. Manatt and Elleman[50] showed by spin-spin decoupling in 3-endo-bromo-camphor that the 3-exo methine proton couples with a proton whose signal appears at 2.33 p.p.m., this latter signal was thus assigned to the C-4 proton.

Flautt and Erman[51] in their detailed study of the P.M.R. spectra of bornane derivatives noted that the exo methine signals

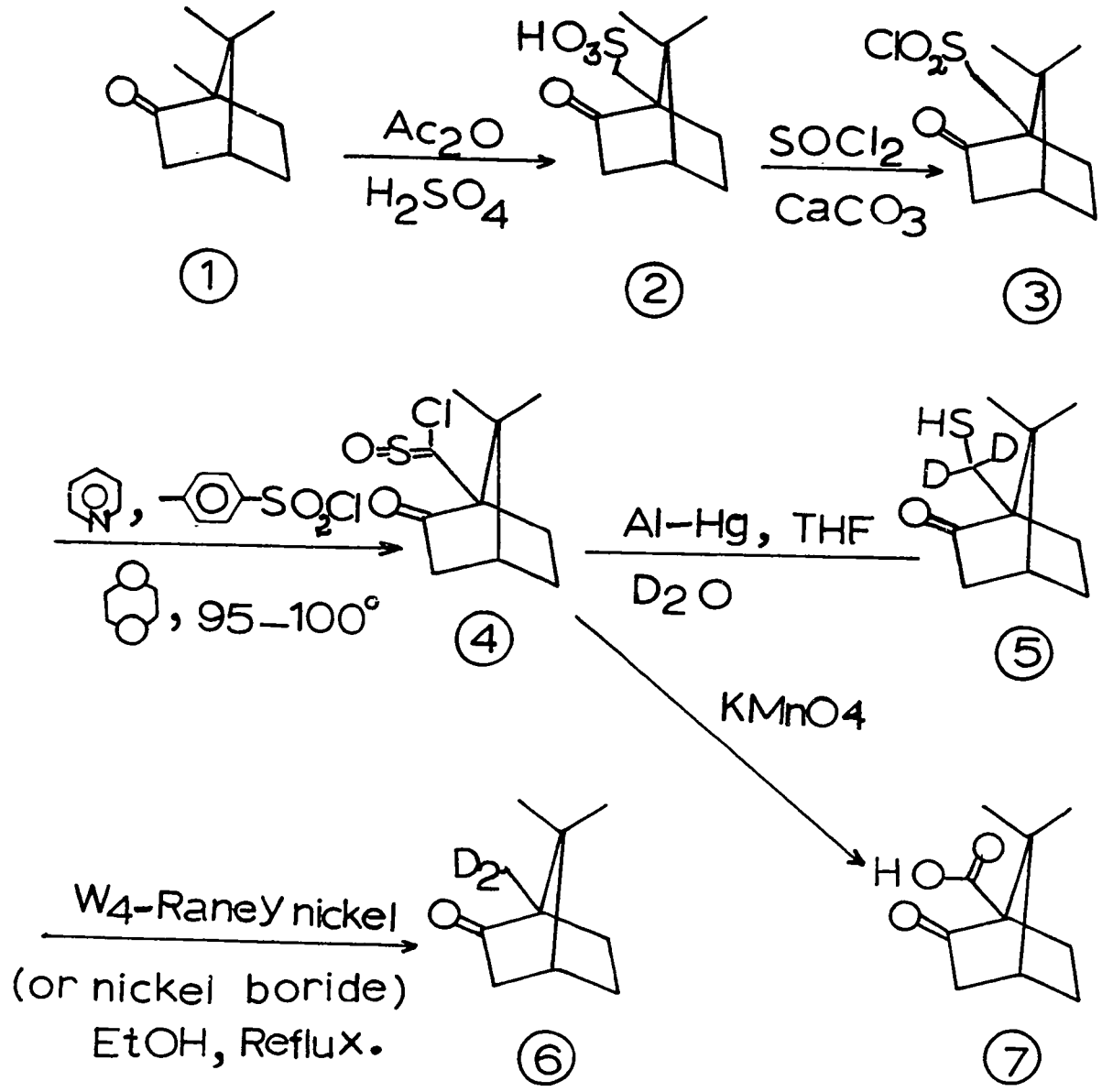
in this series consistently appeared at lower fields compared to the endo methine proton signals. An additional splitting is observed in the exo methine proton signals, with the coupling constant ~1 c.p.s. first described by Anet.[52] Meinwald[53] ascribed this additional splitting to a long range spin-spin coupling between the exo methine proton and a proton four sigma bonds removed from it such that these two protons form the extremities of a "W" pattern through the sigma bonds. Instances of long range coupling through sigma bond systems of this pattern are well known and documented.[54,55] This coupling has been observed[56] in well-resolved spectra of 3-endo-bromocamphor. In accordance to Meinwald's formulation[53] this secondary splitting in the exo methine proton of 3-endo-bromocamphor is ascribed to long range coupling with the C-5 exo proton.

Assignments of methyl signals in camphor derivatives have been ambiguous, mainly because the earlier assignments[49,57] of methyl signals in the P.M.R. spectra of camphor itself have been shown to be erroneous[58] by deuterium labelling of the methyl groups. In order to exploit the P.M.R. method fully in the present investigations, it became desirable to make correct assignments to the methyl signals of 3-halocamphors. A programme of specifically deuterating camphor was undertaken. These labelled camphors have been converted to 3-halocamphors. A description of the labelling procedures follows, prior to the discussion of the P.M.R. spectra.

B. DEUTERATION OF CAMPHOR.

1. At C-10 Methyl Group.

Deuteration at the C-10 methyl group has been achieved by way of camphor-10-sulfonic acid, as shown below:

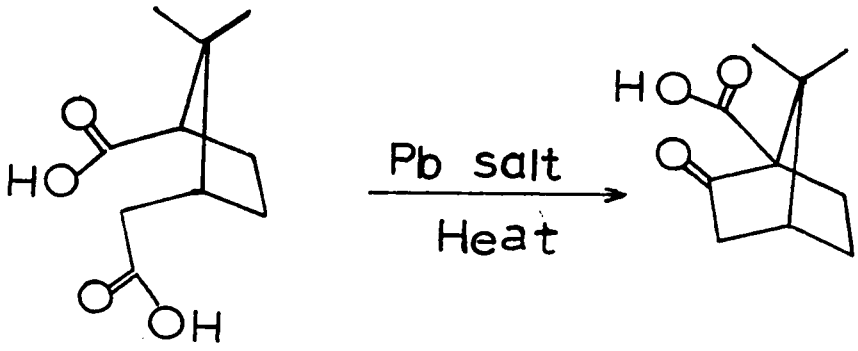


Camphor was converted to camphor-10-sulfonic acid following standard procedures.[59] (In the later stages of this work commercially available D-camphor-10-sulfonic acid was used). This

was converted to its acid chloride with thionyl chloride in the presence of calcium carbonate, a procedure which was found more convenient than the use of phosphorus pentachloride. The sulfonyl chloride (3) was converted to camphor-10-chlorosulfoxide (4) by the action of pyridine in the presence of p-toluenesulfonyl chloride.[60] This reaction first discovered by Wedekind, et al.[61] has been investigated by King and coworkers[62] in recent years and has been shown to go through a sulfene intermediate. Reductive desulfurisation - dehalogenation of(4)in the presence of deuterating agents was regarded as a simple route for labelling the C-10 methyl group. Corey, et al.[63] reduced sulfoxides with aluminium amalgam in aqueous tetrahydrofuran. We found that at room temperature with the chlorosulfoxide(4)this reduction stops at the stage of the known camphor-10-thiol. The conditions were modified to use this reagent for deuteration. The procedure requires small quantities of a relatively cheap deuterium source, viz. deuterium oxide, and the reduction is carried out in tetrahydrofuran solution. Essentially quantitative yields of camphor-10-thiol-10-d_2 are obtained. No reductive coupling of the ketone or reduction to bornanols was observed under these conditions. The thiol (5) on desulfurisation with either W-4 Raney Nickel or nickel boride reagent[64] in refluxing ethanol is converted to camphor-10-d_2. The last step reduces the carbonyl group to a certain extent. This is remedied by oxidation of the crude product by Jones' reagent. By using water at the aluminium amalgam stage and deuterated Raney Nickel for desulfurisation camphor-10-d_1, was prepared. Use of deuterated Raney Nickel for

desulfurisation - reduction of(4) gives camphor-10-d_3.

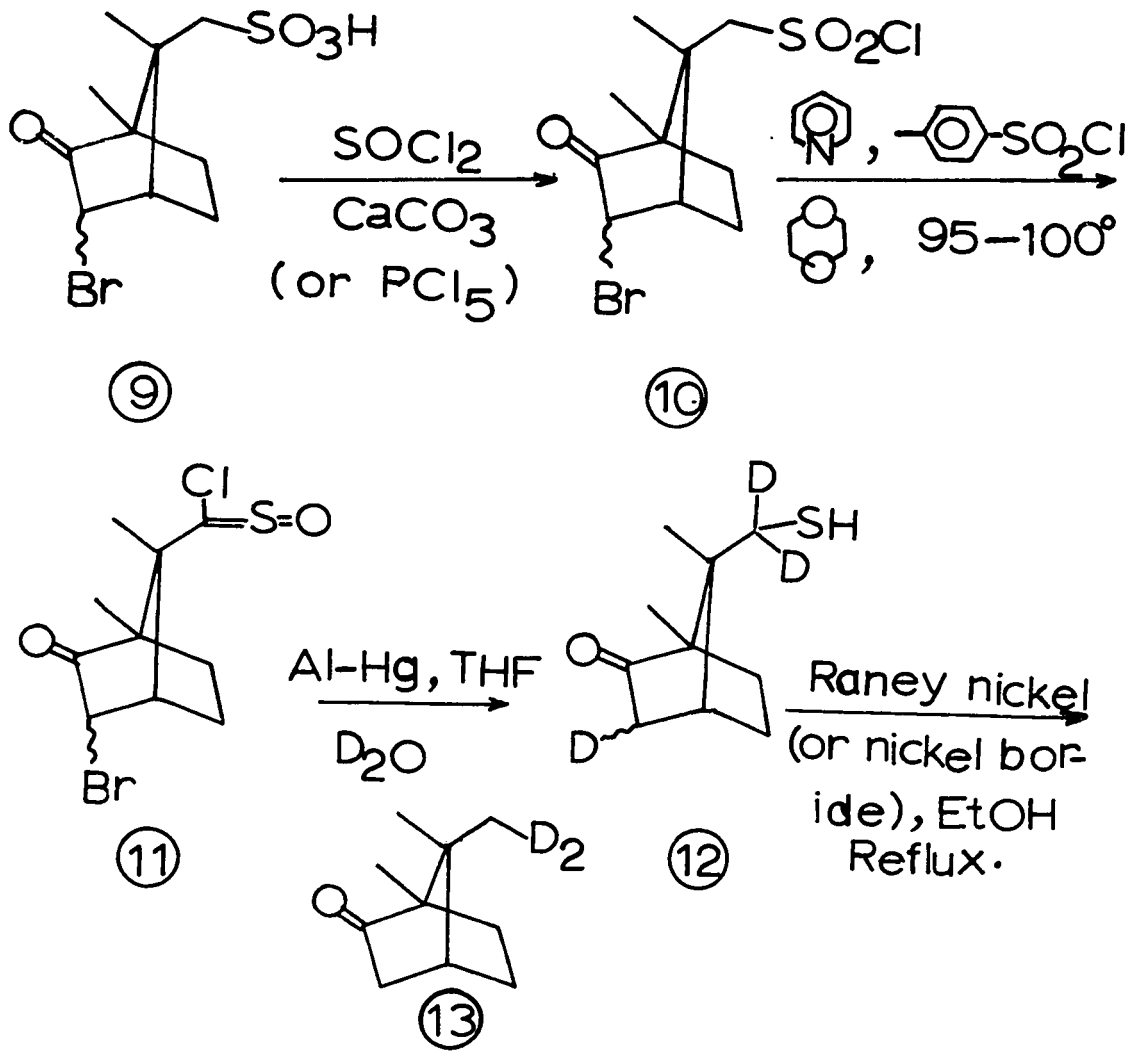
The proof for the location of the deuterium label in the C-10 methyl group by this procedure rests ultimately on the structure of camphor-10-sulfonic acid. Wedekind, et al.[61] converted camphor-10-sulfonic acid through the sequence(2)→(3)→(4)to apocamphane-1-carboxylic acid (7), also known as ketopinic acid. Komppa[65] had earlier proved the structure of ketopinic acid by degradation, and by synthesis. For example ketopinic acid is formed on heating the lead salt of(8) pinophanic acid (structure based on total synthesis):



(8) (7)

2. At C-9 Methyl Group

Entry into C-9 methyl group is attained by way of camphor-9-sulfonic acid. 3-endo-Bromo-D-camphor was sulfonated with chlorosulfonic acid and 3-bromocamphor-9-sulfonic acid (9) was obtained as its sodium or ammonium salt.[66] The sequence of reactions leading to camphor-9-d_2 is shown below.

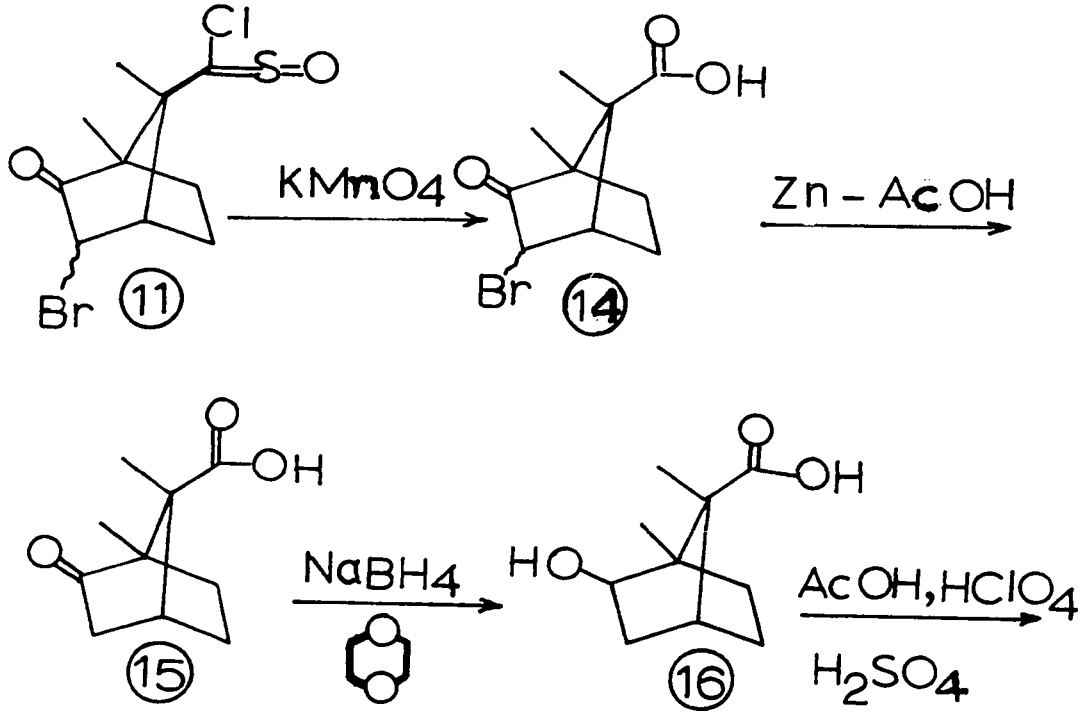


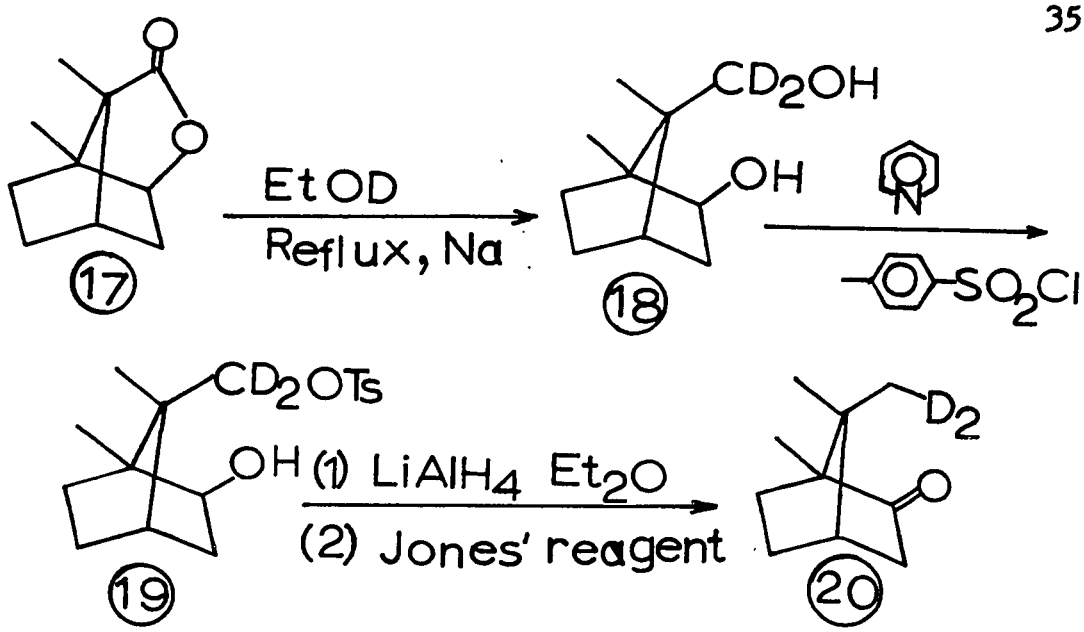
Compound 9 was converted to 3-bromocamphor-9-chlorosulfoxide (11) through a sequence identical to that used for (2)→→(4) earlier. Reduction with aluminium amalgam in tetrahydrofuran-deuterium oxide resulted in simultaneous debromination and reduction to camphor-9-thiol-9,9,3-d_3 in over 90% yield. Desulfurisation with either W-4 Raney Nickel or with nickel boride in boiling ethanol gave camphor-9,9-d_2. The desulfurisation is very sluggish in this case; even after two or three treatments with desulfurising reagent the product still contained considerable thiol. Location of deuterium at the C-9 methyl is proven from

the structure of the sulfonic acid(9). Conversion to chloro-sulfoxide(11), oxidation by alkaline permanganate and debromination with zinc gives trans-isoketopinic acid, (15). The structure of this acid is based on three arguments[67,68] viz. (i) the carboxyl group is not at the bridgehead since the acid is different from ketopinic acid, (ii) reduction of the carbonyl group gives a hydroxy acid 16 which does not form a lactone hence the carboxyl group must be remote from the hydroxyl at C-2, and (iii) the lactone(17) derivable from isomeric 2-hydroxy-cis-apocamphane-8-carboxylic acid on oxidation gives a different carboxylic acid in which the carboxyl group is cis to the carbonyl group.[69]

3. At C-8 Methyl Group.

The C-8 methyl group can be approached by way of the known[68] lactone (17) formed from an acid catalysed rearrangement of 2-hydroxy apocamphane-9-carboxylic acid. The sequence is shown below:

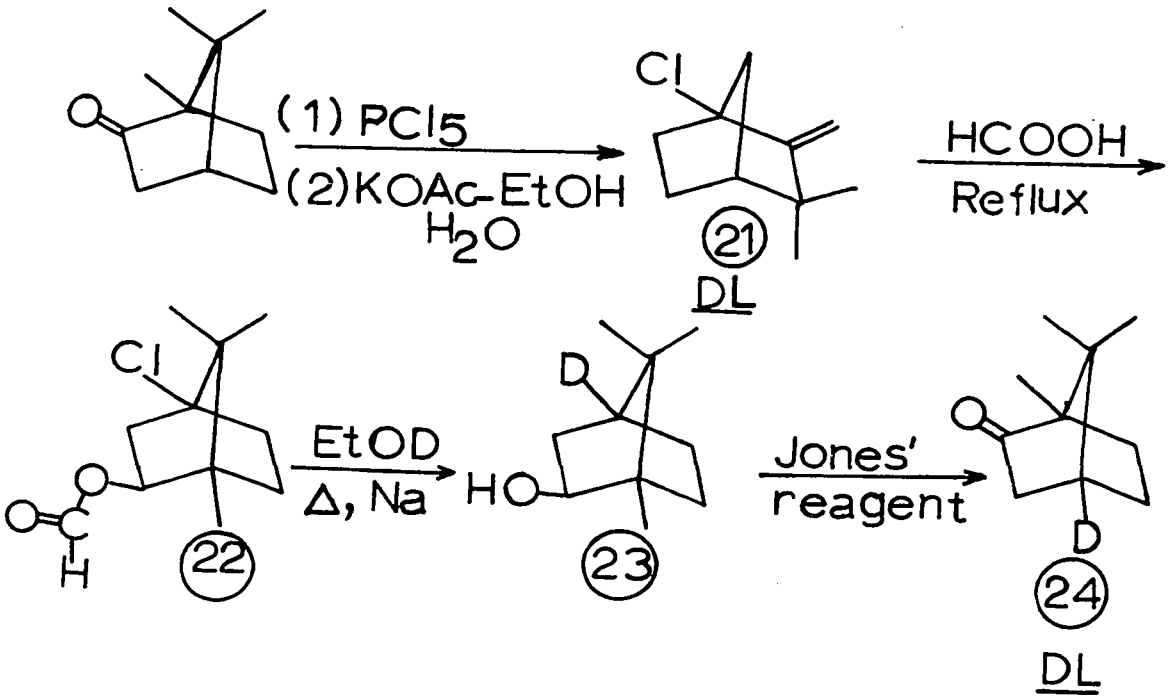




This synthesis has been carried out to the stage of compound (18) only.

4. <u>At C-4 (Bridgehead)</u>

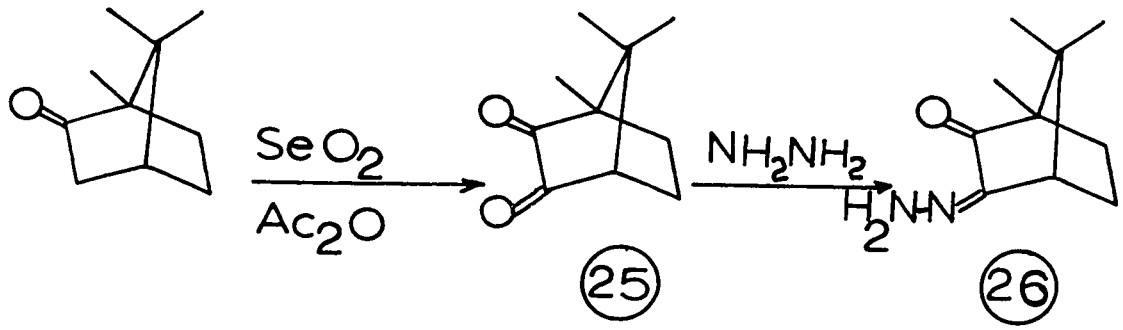
Deuteration at C-4 was done through the known 4-chloro-<u>iso</u> borneol, as follows:



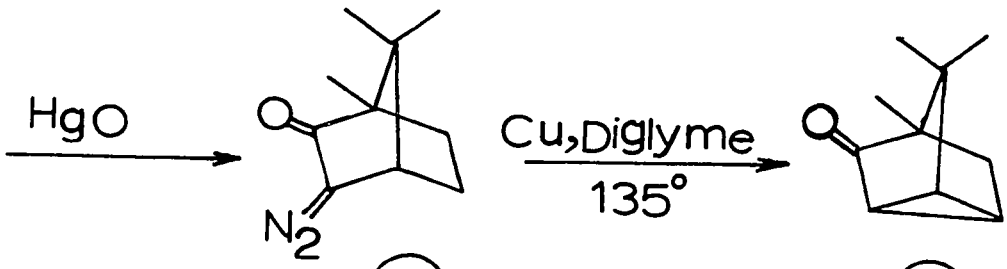
D-camphor was converted to 1-chlorocamphene (21) in two steps.[70] 1-Chlorocamphene was rearranged to 4-chloro*iso*bornyl formate (22) by refluxing with formic acid. After hydrolysis, the bridgehead halogen was replaced by deuterium in a manner analogous to that reported for 4-chloronorborneol.[71] Oxidation with Jones' reagent gave DL-camphor-4-d_1.

5. <u>At C-5</u>

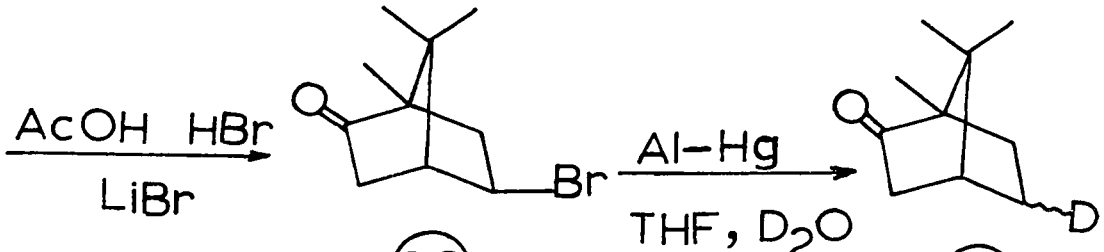
Deuteration at C-5 was done as follows:



25 26



27 28



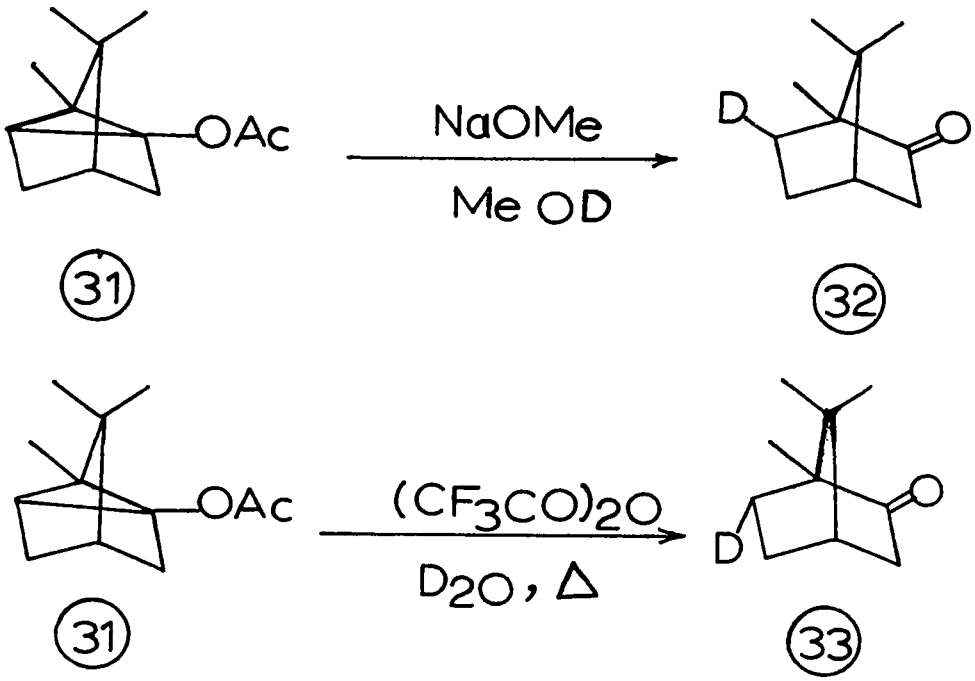
29 30

5-exo-Bromo-d-camphor (29) on debromination with aluminium amalgam and deuterium oxide in tetrahydrofuran gave 5-monodeuteriocamphor (30) shown by conversion to its 3,3-dibromo derivative to be a mixture of 5-endo- and 5-exo-deuteriocamphor by P.M.R. spectroscopy.

For introducing two deuterium atoms at C-5 via its dithioketal, 5-oxo-bornyl acetate has been prepared following the procedure of Malkönen.[72]

6. At C-6

Deuteration at C-6 has been carried out through camphor 2,6-homoenol acetate[73] as follows:*



*Compound (31) has been prepared by W.D. Chambers to whom I am thankful for the sample. Stereochemistry of base catalysed and acid catalysed ring cleavage (32 and 33) products of camphor homoenol acetate has also been investigated by W.D.C.[74]

7. At C-3

D-Camphor-3-d_2 was prepared conveniently from 3,3-dibromo-D-camphor by zinc dehalogenation in acetic acid-d_4.

Stereospecific deuteration at 3-exo and 3-endo positions has also been achieved. This forms part of discussion in Section VIII.

C. 3-Methine Proton in Monohalocamphors

P.M.R. spectra of labelled camphor derivatives are reproduced in plates (1-8).

The chemical shifts and coupling constants of 3-methine protons in 60 Mc/s spectra of 3-monohalogenated camphors obtained in the present work are listed in Table V.

Several useful patterns emerge from these correlations which are summarised below:

(i) The signals from the 3-exo methine proton in all the cases recorded are located at ~0.5 p.p.m. lower field than the signal from 3-endo methine proton with the same substituent at C-3 as previously noted.[51]

(ii) The signal from the exo methine proton is identifiable in the compounds with endo chloro, bromo and iodo substituents by a primary coupling of 5-6 c.p.s. with the proton C-4, and ~1 c.p.s. long range coupling with the C-5 exo proton. This is clearly demonstrated in the spectrum of 3-endo-bromocamphor-4-d, (plate 3), where the signal from 3-exo-methine proton centred at 4.65 p.p.m. does not show the usual 5 c.p.s. coupling with the C-4 proton present in the spectra of the protio analogue. This pattern of a doublet of doublets is diagnostic of the 3-exo-methine proton.

(iii) The signal from the 3-endo methine proton with these substituents (Cl, Br, I) appears as a sharp singlet.

(iv) In the spectra of fluorocamphors there is an additional coupling with the geminal fluorine. Thus, the signal of the 3-exo methine proton of 3-endo-fluorocamphor appears as an eight line pattern in two groups of four lines each, separated by 53-54 c.p.s. The endo methine proton of 3-exo-fluorocamphor appears as a doublet with $J = 53\text{-}54$ c.p.s.

(v) The chemical shift of the 3-methine proton is not related directly to the electronegativity of the geminal halogen substituent. The deshielding effect of the substituent on the 3-exo methine proton (i.e. in endo halocamphors) follows the order $I > F > Br > Cl$.

The 3-methine proton signals from epimeric 3-monohalocamphors are sufficiently characteristic not only to be of value in the identification of individual epimers but are separated well enough in 60 Mc/s spectra to make it possible to estimate the ratios of various epimers in a mixture.

D. Methyl Signals

Table VI summarises the chemical shifts of the methyl signals of camphor and 3-mono- and di-halocamphors. Deuterium labelling of camphor at the C-8[75], C-9[76,77] and C-10[58,77] methyl groups has been reported in the literature. However, spectra of halocamphors with labelled methyls have not been examined so far. Assignments to methyl signals of chloro- and bromocamphors by Tori, et al.[57] were made prior to the availability of labelled camphor and are in error. More recently, Baker and Davis[77] have made assignments to

TABLE V

3-METHINE PROTONS IN P.M.R. OF MONO HALOCAMPHORS[1].

COMPOUND	CHEMICAL SHIFTS p.p.m.	MULTIPLICITY AND COUPLING CONSTANTS	(exoH- endoH) p.p.m.
3-endo-Fluoro-camphor	4.87	Multiplet J3Hx,3F=54cps J3Hx,4H=5cps J3Hx,5Hx=1cps	0.47
3-exo-Fluoro-camphor	4.40	Doublet J3Hx,3F=53cps	
3-endo-Chloro-camphor	4.44	Doublet of Doublets J3Hx,4H=6cps J3Hx,5Hx=1cps	0.54
3-exo-Chloro-camphor	3.90	Singlet	
3-endo-Bromo-camphor	4.65	Doublet of Doublets J3Hx,4H=5cps J3Hx,5Hx=1cps	0.57
3-exo-Bromo-camphor	4.08	Singlet	
3-endo-Iodo-camphor	5.03	Doublet of Doublets J3Hx,4H=5cps J3Hx,5Hx=1cps	0.57
3-exo-Iodo-camphor	4.46	Singlet	

1. All spectra in $CDCl_3$ (30-60%) in Varian A-60 at 60Mc/s, T.M.S. internal standard, x = exo proton.

methyl groups of bromocamphor on the basis of line widths. Their values of chemical shifts reported are in carbon tetrachloride solvent. On examining a sample of 3-endo-bromocamphpr-9-d_1 in carbon tetrachloride solvent we find that the assignments by Baker and Davis are erroneous. The lowest field signal (δ=1.09 p.p.m., in carbon tetrachloride) arises from the C-9 methyl group and not C-8 as reported by them.

1. Methyl Signals in 3-Monohalocamphors

The methyl regions of 3-endo-chloro and 3-endo-bromocamphors are identical in deuteriochloroform, 30-60 percent solution at 60 Mc/s(plates 3 and 4). In both these compounds the respective chemical shifts of the C-8, C-9 and C-10 methyl groups are 0.93, 1.08 and 0.96 p.p.m. The peak positions are not altered in a concentration range of 10-60 percent. Relative to camphor the C-9 methyl group is deshielded by 8 c.p.s. and the C-8 methyl group by 5.5 c.p.s. whereas C-10 is deshielded only by 3.0 c.p.s.

According to Bothner-By and Naar-Colin[78] the main factors affecting shielding in organic molecules are:
(i) the proximity of atoms or groups which donate or withdraw electrons by either an inductive or a resonance effect, (ii) the proximity of groups showing neighbouring diamagnetic anisotropic effects, (iii) the presence of permanent electrical fields within the molecule which might distort the electronic field near the hydrogen nuclei, (iv) the near approach of polarisable groups which leads to a non-vanishing mean square field at the hydrogen nucleus and reduces its shielding.

Effects (i) and (iv) can be neglected in explaining the dif-

TABLE VI[1].

METHYL SIGNALS AND C-4H SIGNALS IN HALOCAMPHORS

COMPOUND	C-8 Me p.p.m.	C-9 Me p.p.m.	C-10 Me p.p.m.	C-4 H p.p.m.
Camphor	0.84	0.95	0.91	2.06
3-endo-Chloro-camphor	0.93	1.08	0.96	2.33
3-exo-Chloro-camphor	1.08	0.97	0.97	2.30
3-endo-Bromo-camphor	0.93	1.08	0.96	2.31
3-exo-Bromo-camphor	1.14	0.97	0.97	2.35
3,3-Dichloro-camphor	1.15	1.11	1.02	2.67
3,3-Dibromo-camphor	1.25	1.14	1.02	2.83

1. All spectra in $CDCl_3$ (30-60%) in Varian A-60 at 60 Mc/s, T.M.S. internal standard.

ference in the relative deshielding between C-9 and C-10 methyl groups. The diagmagnetic anisotropic effects of atom B on atom A are expressed as

$$\sigma_{AB} = \frac{1}{3N_0R_{AB}^3}\Delta\chi_B\left(1-3\cos^2\theta_Z\right)$$

where R (the distance between A and B) must be smaller than 3 A° for this effect to be appreciable. Examination of a Dreiding model shows that the three methyl groups are removed more than 4.5 A° from the halogen atom and hence the effect can be neglected.

This leaves the effect (iii) which probably controls the relative deshielding of the C-9 and C-10 methyl groups in 3-endo halocamphors.

3-exo-Chlorocamphor has a single methyl signal at 1.08 p.p.m. and a signal from two methyl groups at 0.97 p.p.m. 3-exo-Bromocamphor has its low field methyl peak at 1.14 p.p.m. and a two methyl signal at 0.97 p.p.m. Models show that the C-8 methyl group is sufficiently close to the exo-halogen atom in these compounds (< 3 A°) and would be expected to be affected by the magnetic anisotropy of the neighbouring halogen.

2. Methyl Signals in 3,3-Dihalocamphors

Methyl signals of 3,3-dichlorocamphor and 3,3-dibromocamphor (plate 5 and 6) differ with regard to the chemical shifts of the C-8 methyl groups alone. The chemical shifts of C-9 and C-10 methyl groups in these compounds are similar.

The difference in the chemical shifts of the C-8 methyl group of 3,3-dichlorocamphor and of 3,3-dibromocamphor is 6 c.p.s. and presumably reflects the magnetic anisotropy effects of chlor-

ine versus bromine.

E. C-4 Proton

The P.M.R. spectrum of camphor shows an unsymmetrical triplet centred at 2.06 p.p.m. which is missing in camphor-4-d_1, (plate 2). This signal is assigned to the C-4 proton.

In 3-endo-bromocamphor-4-d_1 (plate 3) a multiplet at 2.31 p.p.m. is absent which normally appears at this position in the protio analogue. This is assigned to the C-4 H signal in 3-endo-bromocamphor. Decoupling of this signal in the 100 Mc/s spectrum shows that apart from coupling with the 3-exo methine proton, there is also a coupling with a proton whose signals appear at 1.83 p.p.m. in 3-endo-bromocamphor. We assign this latter signal to the C-5 exo proton. The coupling pattern of the C-4 H in this compound is then a doublet of doublets, $J_{4H,3HX} = J_{4H5HX} = 5$ c.p.s. Decoupling experiments locate the C-5 exo proton in 3-endo-chlorocamphor at 1.85 p.p.m., with $J_{4H5Hx} = 5$ c.p.s.

A characteristic feature of the P.M.R. spectra of 3,3-dihalocamphors is a signal appearing at 2.65-2.85 p.p.m. This signal is absent in 3,3-dibromocamphor-4-d_1 and hence arises from the C-4 H (plate 6). In 3,3-dichloro camphor the C-4 H appears as a multiplet, the pattern is that of an ABX doublet of doublets at 100 Mc/s with $J_{AX} = 3.5$ c.p.s. and $J_{AB} = 0.5$ c.p.s.

The C-4 H in 3,3-dibrom o camphor is centred at 2.83 p.p.m. and appears as the X part of an ABX system, $J_{AX} = 3.5$ c.p.s., $J_{AB} = 0.5$ c.p.s. Apparently, both C-5 exo and endo protons couple with C-4H in 3,3-dihalogen derivatives.

The shape of the C-4 H multiplet is similar in other 3,3-

disubstituted camphors, for instance it appears at 2.62 p.p.m. in bornane-2,3-dione; and at 2.95 p.p.m. in 3-diazocamphor. The coupling pattern can be used to decide the stereochemistry of a deuterium atom at the C-5 position, as seen below.

F. C-5 Protons

Deuteration at the C-5 position via 5-exo-bromocamphor resulted in introduction of one deuterium atom. The stereochemistry of this deuterium was decided by conversion of the product into its 3,3-dibromo derivative. The C-4 H signal of this derivative is expected to collapse into a doublet, $J = 0.5$ c.p.s. if the deuterium were exclusively exo at C-5, and a doublet with $J = 3.5$ c.p.s. if the deuterium were endo. The P.M.R. spectrum of 3,3-dibromocamphor-5-d_1 shows its C-4 H signal as a broad singlet with half height width = 6 c.p.s. It is therefore concluded that deuteration has resulted in about equal distribution at C-5 exo and endo-positions.

G. C-3 Protons.

Comparison of the spectra of 3-deuterated camphors reveals that the 3-exo proton signal is a multiplet, resulting from a geminal coupling of 22 c.p.s. with 3-endo proton, a vicinal coupling with C-4 H, $J = 5$ c.p.s. and a long range coupling with C-5 exo proton, ~ 2 c.p.s. One half of this multiplet is centered at 2.53 p.p.m. and is recognisable in the P.M.R. spectrum of camphor (plate 1). The centre of the C-3 exo proton multiplet is at 2.33 p.p.m. The C-3 endo proton in camphor is centred at 1.78 p.p.m.

H. Conclusion

Analysis of complex mixtures of monohalogenated camphors can be done by recourse to the 3-methine signals in their P.M.R. spectra. Dihalocamphors resulting from the halogenation of monohalocamphors can be recognised and estimated from the locations of the C-4 H signals. Based on the spectra of the dichloro and dibromocamphors, the signal from 3-exo-bromo-3-endo-chloro epimer is expected to appear 10 c.p.s. lower field than the signal from 3-endo-bromo-3-exo-chlorocamphor.

When only two epimeric halocamphors are present in a mixture their amounts can also be estimated from the intensities of the methyl signals, the C-8 methyl signal in the epimer with bromine exo would be clearly separated from the rest of the methyl signals.

IV

HALOGENATION OF 3-MONOHALOCAMPHORS AND THEIR ENOL DERIVATIVES

A. INTRODUCTION

A study of the physical properties of pure halocamphors (section II and III) led to the choice of P.M.R. methods as most suitable for estimating the proportions of epimeric 3-bromo-3-chlorocamphors in a mixture that might also contain 3-monohalocamphors and camphor. Using the C-4 proton region of 3,3-dichloro- and 3,3-dibromocamphors as a probe this method is able to detect less than 2% of the minor component in a mixture. The reproducibility of the method using differential integration of C-4 H signals is better than 2%. This sets a limit of precision to the analytical figures.

The transition state in the halogenation of 3-monohalocamphors would be expected to be similar to that of camphor itself with regard to the stereoelectronic factors. There is reason to believe that in analogous systems, such as the electrophilic addition to norbornenes, orbital overlap favours exo-approach of the reagent.* The transition states for camphor and monohalocamphors differ with regard to the steric factors however.

In the transition state for halogenation of 3-monohalocamphors the exo side is expected to be more crowded due to the C-8 methyl

* A more detailed discussion appears in Section IX.

group and C-3 halogen substituent compared to the transition state in the halogenation of camphor where the substituent at C-3 being hydrogen has smaller steric requirements. This is schematically represented in Fig. 9 below.

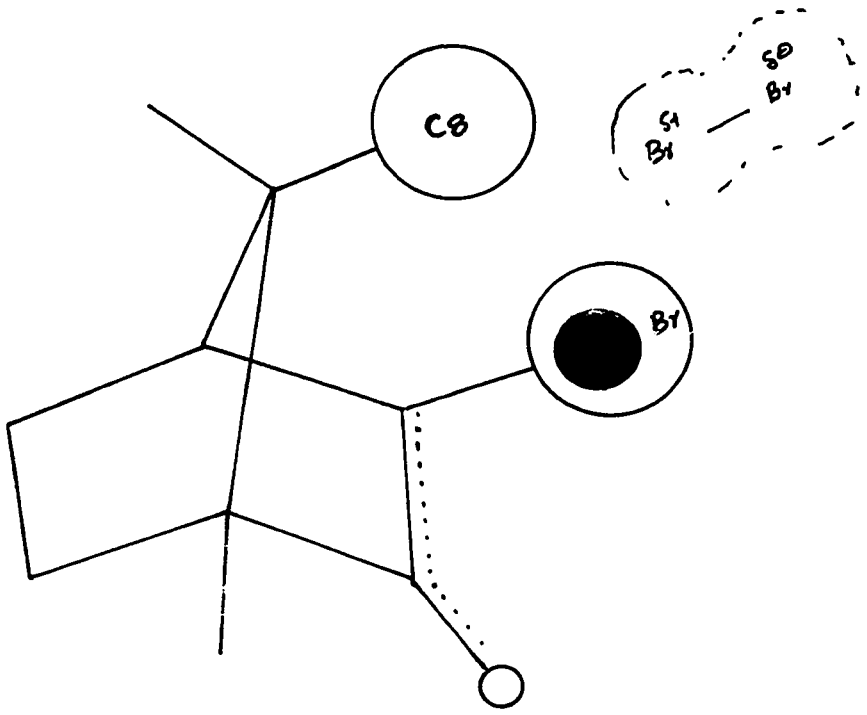


Fig. 9.

exo- Approach of reagent in 'planar' transition state of 3-monobromocamphor. Inner solid circle at C-3 compares transition state for the halogenation of camphor.

In the studies on the halogenation of monohalocamphors and their enol derivatives the crude neutral organic reaction product was directly examined by P.M.R. spectroscopy to obtain the relative proportions of epimeric 3-bromo-3-chlorocamphors judged from the

intensities of C-4 proton signals appearing between 2.65 and 2.85 p.p.m. An internal check on the extent of halogenation can be made from the intensities of C-3 methine proton signals of the 3-monohalocamphors. Plate 10 shows P.M.R. spectrum of a typical reaction product. The neutral organic products from the reaction were also subjected to thin layer chromatography as a check on the nature of the components, thus affording evidence that the products were indeed the 3-monohalo- and 3,3-dihalocamphors.

Four sets of studies were planned - (i) direct halogenation such as was studied by Lowry (ii) halogenation under conditions established to be kinetically controlled (iii) halogenation of enolates of monohalocamphors generated by the action of strong bases, with a large excess of halogenating agent to produce kinetically controlled conditions and (iv) halogenation of enol acetates of 3-chloro- and 3-bromocamphors.

B. DIRECT HALOGENATION

Both 3-endo-chloro-D-camphor and 3-endo-bromo-D-camphor were halogenated. Results are summarised in Table VII.

C. HALOGENATION IN GLACIAL ACETIC ACID - POTASSIUM ACETATE

Results are listed in Table VII.

1. BROMINATION OF 3-endo-CHLORO-D-CAMPHOR*

A mixture of 3-endo-chlorocamphor, bromine, potassium acetate

* There was no sign of bromination with bromine in glacial acetic acid-potassium acetate for two hours on a steam bath; chlorocamphor treated with hydrobromic acid in glacial acetic acid followed by treatment with bromine-acetic acid-potassium acetate mixture, or on heating a mixture of chlorocamphor-bromine-acetic acid-potassium acetate in a sealed tube at 100 ± 2°C for four hours.

TABLE VII

HALOGENATION OF 3-MONOHALOCAMPHORS

NO.	SUBSTRATE mg.	REAGENT	CONDITIONS	CRUDE YIELD %	EPIMERIC COMPOSITION	
					exo-Bromo-endo-chlorocamphor, %	endo-Bromo-exo-chlorocamphor, %
1	3-endo-Chloro-D-camphor 932.4	Bromine ~900 mg.	95 -100° 4 hrs.	98.5	41	59
2	---"--- 304	Bromine ~450 mg.	Sealed Tube 105±2° 1 hr.	95.7	42	58
3	---"--- 308	---"--- ~450 mg., HBr (traces)	Sealed Tube 105±2° 12 hrs.	92.5	39	61
4	---"--- 1623	---"--- 1520 mg., AcOH, $CHCl_3$, HBr	95 -100° 24 hrs.	96.6	37	63
5	---"--- 247.5	---"--- 310 mg., KOAc ~1000 mg. HOAc 10 ml.	Sealed Tube 120°, 4 hrs.	41*	45.8	54.2

TABLE VII

HALOGENATION OF 3-MONOHALOCAMPHORS

NO.	SUBSTRATE mg.	REAGENT	CONDITIONS	CRUDE YIELD %	EPIMERIC COMPOSITION exo-Bromo-endo-chlorocamphor, %	EPIMERIC COMPOSITION endo-Bromo-exo-chlorocamphor, %
6	3-endo-Chloro-D-camphor 281.2	Bromine 480 mg. KOAc ~ 600 mg. HOAC 7.2 ml.	Sealed Tube 120°, 1 hr.	50*	39.2	60.8
7	---"--- 281	---"---480 mg. KOAc ~1200 mg. HOAC 11.2 ml.	Sealed Tube 120°, 1 hr.	42*	43	57
8	---"--- 281.5	---"---480 mg. KOAc ~1800 mg. HOAc 15.2 ml.	Sealed Tube 120°, 1 hr.	49*	46	54
9	---"--- 381.5	---"--- 1000 mg., KOAc ~1000 mg., "75% CH_3CN" 100 ml.	25±0.01° 110 hrs. 45 min.	25*	20	80
10	3-endo-Bromo-D-camphor 462-2	Sulfuryl Chloride 0.19 ml.	Sealed Tube 110±2°, 4 hrs.	96.5	56.8	43.2
11	---"--- 481	---"--- 0.2 ml.	Sealed Tube 110±2°, 24 hrs.	98	58	42

TABLE VII

HALOGENATION OF 3-MONOHALOCAMPHORS

NO.	SUBSTRATE mg.	REAGENT	CONDITIONS	CRUDE YIELD %	EPIMERIC COMPOSITION exo-Bromo-endo-chlorocamphor, %	EPIMERIC COMPOSITION endo-Bromo-exo-chlorocamphor, %
12	3-endo-Bromo-D-camphor 347.2	Chlorine~97.6 mg., KOAc ~600 mg. AcOH 7.2 ml.	Sealed Tube 120°, 1 hr.	18*	60	40
13	---"--- 347.6	---"--- 97.6 mg. KOAc ~1200 mg. AcOH 11.2 ml.	Sealed Tube 120°, 1 hr.	20*	61	39
14	---"--- 348.5	---"--- 97.6 mg. KOAc ~1800 mg. AcOH 15.2 ml.	Sealed Tube 120°, 1 hr.	26.8*	59.8	40.2

* These are yields of percent chlorobromo epimers formed and are calculated from the ratio of C-3 methine proton (unreacted substrate) and C-4 proton of dihalocamphors (products).

"75%" CH_3CN is a solution of 75 parts by volume acetonitrile and 25 parts by volume water.

and glacial acetic acid was heated in a sealed tube at 120° for one to four hours. Four independent runs were made with varying amounts of potassium acetate which was in excess of that required for neutralising the theoretical amount of hydrobromic acid formed in the mixture. The amount of bromine was more than required for complete bromination of chlorocamphor used. In spite of this the extent of bromination of chlorocamphor was only 40-50 percent although no free bromine remained at the end of the reaction period. Control runs with bromine and potassium acetate in glacial acetic acid (without chlorocamphor) at 120° for four hours showed complete disappearance of bromine (no bromine colour left, negative starch-iodide test). An inorganic salt crystallised out of the solution and was shown to be potassium bromide accounting for over 90% of both atoms of $\underline{Br_2}$ as bromide anion. P.M.R. spectra of the crude reaction product (liquid) showed a signal at 2.05 p.p.m. arising from acetate methyl and a feeble signal at 4.66 p.p.m. presumably arising from $-O-\underline{CH_2}-\overset{O}{\overset{\|}{C}}-O$ group. To confirm this observation a control experiment was carried out with larger proportion of bromine to acetic acid. The presence of 4.66 p.p.m. signal was confirmed in ether extract of the reaction product.*

---

* The observations can be rationalised as follows:

$$Br_2 + CH_3COOH \longrightarrow BrCH_2-\overset{O}{\overset{\|}{C}}-OH + HBr$$

$$BrCH_2-\overset{O}{\overset{\|}{C}}-OH + KOAc \longrightarrow CH_3\overset{O}{\overset{\|}{C}}-O-CH_2-\overset{O}{\overset{\|}{C}}-OH + KBr$$

This would account for the total conversion of bromine into bromide anion as well as for the low field signal in the P.M.R. spectrum of the products.

The proportion of 3-exo-bromo-3-endo-chloro epimer in the mixture of epimeric 3-bromo-3-chlorocamphors was found to be 42.5 ± 3 mole percent under these conditions, (entries 5, 6 and 7 of Table VII). In a control run with 3,3-dibromocamphor, potassium acetate and glacial acetic acid at 120° for four hours 99% of 3,3-dibromocamphor was recovered. There was no evidence of debromination whatsoever.

Bromination of 3-endo-chloro-D-camphor was also carried out under carefully controlled conditions in "75% Acetonitrile" (i.e. 75 parts by volume acetonitrile and 25 parts by volume water mixed together) with bromine in the presence of potassium acetate at 25° ± 0.01°C (entry 9 of Table VII). These conditions are precisely those under which the kinetics of debromination of the epimeric chlorobromocamphors were studied in a later section. After 110 hours and 45 min. the amount of epimeric dihalocamphors formed was 25 mole percent (the rest unreacted). The proportion of 3-exo-bromo-3-endo-chlorocamphor was 20 mole percent of the epimeric dihalocamphors.

2. CHLORINATION OF 3-endo-BROMO-D-CAMPHOR

Chlorination of 3-endo-bromo-D-camphor in glacial acetic acid-potassium acetate buffer at 120° was a much less efficient reaction compared to bromination of chlorocamphor; even with excess chlorine only 18-27 percent chlorination of 3-bromocamphor occurred. However, as in the case of bromination, chlorine was consumed completely by the end of the reaction period. Control experiments demonstrated the conversion of molecular chlorine to

chloride anion, isolated as potassium chloride.

The proportion of 3-exo-bromo-3-endo-chlorocamphor under these conditions was 60 mole percent of the epimeric mixture, in three independent runs (average figure, entries 12, 13 and 14 of Table VII).

D. HALOGENATION OF ENOLATES OF MONOHALOCAMPHORS

Results of these experiments are summarised in Table VIII.

1. SODIUM ENOLATES

The enolate of 3-bromocamphor was generated from 3-endo-bromo-D-camphor in tetrahydrofuran solution by sodium hydride. The reaction is slow, requires refluxing for a period of two hours with continuous stirring, and the solubility of the enolate in tetrahydrofuran is rather low at low temperatures. The enolate was allowed to react with chlorine by introducing a rapid stream of dried chlorine gas while the mass was stirred at the desired temperature. The product contained some monobromocamphor, an unidentified material showing absorption in the region of 3.3-4.2 p.p.m. and epimeric 3-bromo-3-chlorocamphors. The proportion of 3-exo-bromo-3-endo-chlorocamphor was 33.5 ± 1.5 mole percent at -70°C (entries 2 and 3, Table VIII).

To ascertain that the signals at 2.65 - 2.85 p.p.m. were in fact from epimeric chlorobromocamphors and not from the unidentified impurity, the material was subjected to chromatography on neutral alumina, followed by recrystallisation. A fraction free of monohalocamphors and other impurities was obtained, and proved by dehalogenation, elemental analysis and P.M.R. spectroscopy to be epimeric chlorobromocamphors, with the propor-

tion of 3-exo-bromo-3-endo-chloro-D-camphor being 35 mole percent of the epimer mixture. This figure is essentially the same as obtained from the integration of the C-4 proton signal in the neutral crude product.

2. LITHIUM ENOLATES

The enolate of bromocamphor or chlorocamphor was generated using 1.5-2.0 mole equivalents of an alkyllithium in tetrahydrofuran solution under nitrogen giving an enolate concentration of 0.05 M to 0.15 M. The reaction is exothermic and is carried out at room temperature without cooling (depending on the rate of addition of the alkyllithium at times the reflux temperature of tetrahydrofuran was reached). Another 0.5-1.0 hour was allowed before the mass was cooled to the desired temperature, and the halogenating reagent added. The reagent was introduced as fast as possible while the mass was stirred under nitrogen. The amount of available halogen was in excess of that required for reacting with the total base present in the system. With molecular halogen as the reagent the solutions were faintly acidic or neutral at the end of the reaction. The neutral products were extracted with petroleum ether and the ratios of epimeric chlorobromocamphors determined by integration of areas under the 2.65-2.85 p.p.m. region.

Chlorination of the lithium enolate of bromocamphor with chlorine was carried out at two temperatures (entries 4, 5 and 6, Table VIII), and with a series of positive chlorine compounds (viz. t-butyl hypochlorite, N-chlorosuccinimide, sulfuryl chloride and adducts of chlorine with tertiary amines) at different temp-

eratures.

Bromination of the lithium enolate of chlorocamphor was done by bromine and by N-bromosuccinimide (entries 18-20, Table VIII).

To establish that the first formed epimer ratio was not altered by the carbon base present in the system (before it came in contact with excess reagent and got destroyed) a control experiment was carried out (entry 5, Table VIII). The enolate was added in a reverse manner, under nitrogen, to an excess of chlorine solution so that chlorine was always in excess throughout, leaving no chance for the carbon base to attack the first formed dihaloketone. The results show that the epimer ratio from this experiment is identical, within the limits of precision of the analytical procedure, with the result (entry No. 4) from the normal procedure under otherwise identical conditions. In an experiment in which the enolate was generated with methyllithium using less than one equivalent of base, so that the ketone was in excess (entry No. 9 and 9a, Table VIII), the epimer ratio was altered from a normal case (excess base, entry No. 8).

E. HALOGENATION OF ENOL ACETATES OF 3-CHLORO AND 3-BROMOCAMPHORS

Enol acetates of 3-chloro- and 3-bromocamphors were prepared by acylation of the lithium enolate of 3-chloro- and 3-bromocamphors. These are new compounds whose preparation, characterisation and properties are described in greater length along with camphor enol acetate in Section VII.

3-Halocamphor enol acetates react very slowly with halogens compared to the enolates. This reactivity is also much slower than that of camphor enol acetate. Catalysts were needed for this halo-

TABLE VIII

HALOGENATION OF SODIUM AND LITHIUM ENOLATES OF 3-HALOCAMPHORS

NO.	SUBSTRATE	BASE	REAGENT	CONDITIONS	PROPORTIONS OF DIHALOEPIMERS exo-Bromo endo-Chloro %	endo-Bromo exo-Chloro %
1	3-endo-Br-Camphor	Sodium Hydride	Chlorine	0°C	44.3	55.7
2	---"---	---"---	---"---	-70°C	35.0	65.0
3	---"---	---"---	---"---	-70°C	32.5	67.5
4	---"---	n BuLi	Cl_2 in CCl_4	25°±5°C	33.8	66.2
* 5	---"---	---"---	---"---	25°±1°C	37.0	63.0
6	---"---	---"---	---"---	-70°C	39.8	60.2
7	---"---	---"---	t-BuOCl	25°C	28.5	71.5
8	---"---	---"---	---"---	-70°C	18.8	81.2
** 9	---"---	MeLi	---"---	-70°C	30.6	69.4
** 9a	---"---	n BuLi	---"---	-70°C	28.0	72.0
10	---"---	MeLi	---"---	-100°C	16.8	83.2
11	---"---	---"---	N-Cl-Succinimide	25°C	38.0	62.0

TABLE VIII

HALOGENATION OF SODIUM AND LITHIUM ENOLATES OF 3-HALOCAMPHORS

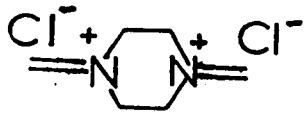
NO.	SUBSTRATE	BASE	REAGENT	CONDITIONS	PROPORTIONS OF DIHALOEPIMERS exo-Bromo endo-Chloro %	endo-Bromo exo-Chloro %
12	3-endo-Br-Camphor	MeLi	N-Cl-Succinimide	-70°C	25.0	75.0
13	---"---	---"---	SO_2Cl_2	25°C	76.9	23.1
14	---"---	---"---	---"---	-70°C	73.5	26.5
15	---"---	t-BuLi	Dabco-Cl_2 #	25°C	No Reaction	
16	---"---	---"---	2,6-lutidine-Cl_2	25°C	77	23
17	---"---	---"---	Triethylamine-Cl_2	25°C	No Reaction	
18	3-endo-Cl-Camphor	n-BuLi	Br_2 in CCl_4	25°C	64.2	35.8
19	---"---	PhLi	---"---	25°C	61.2	38.8
20	---"---	t-BuLi	N-Br-Succinimide	25°C	65.5	34.5

FOOTNOTES FOR TABLE VIII

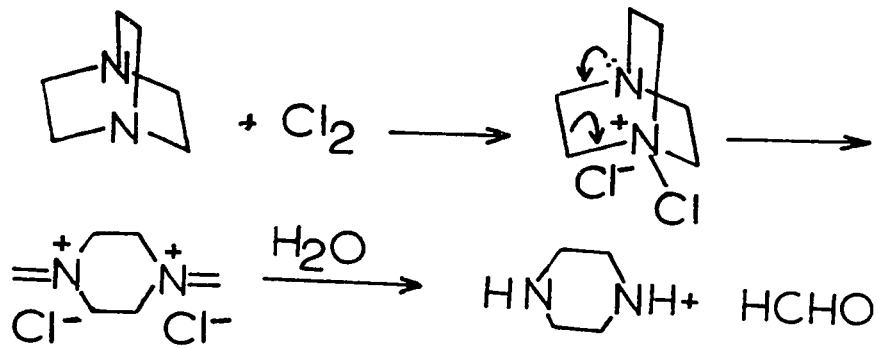
*5 CONTROL EXPERIMENT. Reverse addition of enolate to excess chlorine solution.

**9,9a Base less than one equivalent. Ketone in excess.

The chlorine adduct of triethylene diamine (dabco) is an unstable crystalline solid which decomposes into



at room temperature in a few minutes after preparation. This was identified from formaldehyde formed on bringing in contact with water. The reaction is visualised as an oxidative fragmentation:-



Similar behaviour was observed with bromine. Analogous reactions have recently been reported in the literature.[152]

genation. Lithium halides, mercuric oxide and iodine were found to be good catalysts and were used in the study of halogenation of these vinylic halide esters. The results are given in Table IX.

1. 3-BROMO-D-CAMPHOR ENOLACETATE

Chlorination was done by molecular chlorine, sulfuryl chloride and N-chlorosuccinimide in protic and non protic solvents, with or without catalysts.

In acetonitrile using lithium chloride as catalyst there was no change in the ratio of epimeric chlorobromocamphors from -45° to $+70^{\circ}$, with chlorine as reagent (entries 3, 4 and 5, Table IX). In all the cases of chlorination by molecular chlorine the proportion of 3-exo-bromo-3-endo-chloro-D-camphor was above 90 mole percent, and became $\sim$100 mole percent (entry No. 6) in iodine catalysed chlorination in carbon tetrachloride. Sulfuryl chloride and N-chlorosuccinimide gave only 80 mole percent of 3-exo-bromo-3-endo-chloro-camphor.

2. 3-CHLORO-D-CAMPHOR ENOL ACETATE

Bromination either in carbon tetrachloride-glacial acetic acid mixture (entry 11) or in carbon tetrachloride alone (entry 12) gave 5.5 ± 1 mole percent of 3-exo-bromo-3-endo-chlorocamphor.

F. DISCUSSION

Direct halogenation of 3-monohalocamphors under the conditions that Lowry used is an acid catalysed reaction involving the enol of the halocamphor as an intermediate. Bromination of 3-chlorocamphor by molecular bromine under an open condenser at 95°-100° (entry 1, Table VII) or in a sealed tube at 105° (entries 2 and 3,

TABLE IX

HALOGENATION OF 3-HALOCAMPHOR ENOL ACETATES

NO.	SUBSTRATE	REAGENT	CONDITIONS	PROPORTIONS OF CHLOROBROMOCAMPHORS	
				exo-Bromo endo-chloro %	endo-Bromo exo-chloro %
1	3-bromo-D-camphor enol acetate	Cl_2 in CCl_4-ACOH LiBr (cat.)	25° 12 hrs.	94	6
2	---"---	Cl_2 in CCl_4-ACOH HgO, LiCl (cat.)	25° 24 hrs.	93	7
3	---"---	Cl_2 in CH_3CN LiCl (cat.)	70° 4 hrs.	91.4	8.6
4	---"---	---"---	24.5° 4 hrs.	90.0	10.0
5	---"---	---"---	-45°±2° 4 hrs.	92.3	7.7
6	---"---	Cl_2 in CCl_4 I_2 (cat.)	25° 4 hrs.	$\gg 99$	~ 0.0
7	---"---	SO_2Cl_2 in CCl_4	Reflux 4 hrs.	No reaction	

TABLE IX

HALOGENATION OF 3-HALOCAMPHOR ENOL ACETATES

NO.	SUBSTRATE	REAGENT	CONDITIONS	PROPORTIONS OF CHLOROBROMOCAMPHORS	
				exo-Bromo endo-chloro %	endo-Bromo exo-chloro %
8	3-bromo-D-camphor enol acetate	SO_2Cl_2 LiCl (cat.)	Reflux 3 hrs.	80	20
9	---"---	N-Cl-Succinimide in CCl_4	Reflux 5 hrs.	No reaction	
10	---"---	N-Cl-Succinimide in Dioxane-H_2O	Steam Bath 10 hrs.	80	20
11	3-chloro-D-camphor enol acetate	Br_2 in CCl_4-ACOH HgO, LiCl (cat.)	25° 10 hrs.	6.4	93.6
12	---"---	Br_2 in CCl_4 I_2 (cat.)	25° 3 hrs.	5	95

Table VII) gave the same proportion of epimeric chlorobromocamphors, the 3-exo-bromo-3-endo-chlorocamphor being 40±1 mole percent. Since this ratio remains unaltered in the presence of added hydrobromic acid (entry 3, Table VII) and over an extended time period, apparently the first formed products are reasonably stable to hydrobromic acid. The somewhat smaller proportions of 3-exo-bromo-3-endo-chloro epimer obtained in glacial acetic acid-chloroform mixture probably reflects the effect of solvent on the epimer ratio. In all these cases it is observed that more of the entering halogen (bromine in this case) enters from a direction so as to give larger amounts of the epimer containing bromine endo. The transition state for halogenation of the enol might be more sensitive to steric factors than the transition state for enolate halogenation due to lower nucleophilicity of the enol as against that of the enolate. If this is true, one would expect a greater endo preference for the entering group since the presence of the C-8 methyl group and the 3-halogen substituent make the exo side highly crowded. This effect should be particularly noticeable when the entering group is also large. One would expect to notice this effect for entering bromine (van der Waal's radius, r=1.95A) more than for entering chlorine (r = 1.8A).[79] As is expected there is a preference for bromine entering from the endo side over that from the exo by a factor of 1.5 to 1.

Chlorination of bromocamphor was done by sulfuryl chloride. There is evidence[80] that chlorination of ketones by this reagent proceeds through an acid catalysed ionic mechanism. Sulfuryl

chloride is known to act as a source of electrophilic chlorine.[81] It can therefore be deduced that in the chlorination of bromocamphor by sulfuryl chloride the reactive intermediate will be the enol of bromocamphor. As expected the entering halogen (chlorine in this case) is preferred 1.5 times more from the endo direction than from the exo direction.

Halogenation of 3-monohalocamphors in acetic acid-potassium acetate would be expected to go through an enol rather than an enolate intermediate. This is expected from the acidity of these haloketones. Although we do not have direct figures of pK_A's for 3-halocamphors, we expect these to be in the range of 15 to 20 pK units; conversely stated, the enolate is a very strong base and in a protic medium such as glacial acetic acid would tend to exist largely in O-protonated form. In this system (acetic acid-acetate) at 120° the product distribution reveals that entry of the halogen atom from the endo side is favoured to the same extent as in the case of direct halogenation. Under these conditions, 3,3-dihalocamphors have been demonstrated to be stable to the buffer system and do not get epimerised. The product ratios are therefore truly representative of the first formed (kinetically controlled) products. Under more carefully controlled conditions, viz. in aqueous acetonitrile with potassium acetate buffer, bromination of 3-endo-chlorocamphor at 25° ± 0.01°C gave as much as 80 mole percent of product (entry 9, Table VII) arising from endo entry of the reagent. The preference for endo entry of the reagent is 4 times that for exo entry, as against 1.5 endo: 1 exo in glacial acetic acid-acetate system.

The marked change in the epimer ratio probably has its origin in at least two factors (a) solvent polarity and (b) temperature. Acetonitrile is much more polar than glacial acetic acid, this can influence the solvation of the intermediate as well as the reagent. Temperature influences would be related to the shape of temperature-rate curves for endo entry versus exo entry.

These results seem to bear out the contention that in the halogenation of halocamphors involving an enol intermediate the steric requirements of the transition state predominate over the stereoelectronic preferences. If this is true, the halogenation of enol esters would provide a fairly good model for this contention, and one would predict that a much greater steric influence would be present in this case. Halogenation of enol esters of 3-halocamphors justify this view. The entry of the halogen from endo side is at least four times preferred over exo entry (actually the preference for endo entry varies by a factor of 4 to over 99 compared to 1 for exo entry). There seems to be some effect of solvent polarity, the polar solvents gave lesser selectivity. This effect could be due to the nature of the halogenating species involved.[82-84] In non-polar media iodine catalysed halogenation presumably involved molecular aggregates[85] accounting for higher selectivity because of greater steric requirements of the halogenating species.

The fact that chlorination of bromocamphor enol acetate catalysed by iodine in carbon tetrachloride gave ~100% entry of chlorine from endo side whereas bromination of chlorocamphor enol acetate under these conditions gave only 95% entry of bromine

from endo side can be rationalised from the considerations of the structure of these vinylic ester halides. In a Dreiding model the C-8 methyl group and C-3 bromine make the exo side very crowded, whereas, with chlorine at C-3 the crowding is less severe. This could account for 100% of entering halogen going from endo side in the former case and only ~95% in the latter case.

The directional control is completely reversed in the case of the halogenation of sodium or lithium enolates of camphor. Bromination of lithium enolate of chlorocamphor by bromine or by N-bromosuccinimide at 25° gave a product in which over 60% of bromine enters from the exo side. When either the sodium enolate or the lithium enolate of bromocamphor was chlorinated by molecular chlorine, over 60% of product with entering halogen (chlorine) coming from the exo side was formed. A still larger amount of epimer with the entering group coming from the exo side is formed with positive chlorine compounds such as t-butyl-hypochlorite and N-chlorosuccinimide. Control experiments show that the conditions are kinetically controlled. These results then show a direction control exactly opposite to that found in the halogenation of an enol or an enolester intermediate.

We offer the suggestion that in the halogenation of enolates the stereoelectronic factor* which favors exo entry of the reagent is most important in the transition state for halogenation. Since the nucleophilicity of enolates is very high, the carbon halogen bond begins to form at a greater distance where the C-8 methyl

* For speculations regarding the nature of this so-called stereoelectronic factor see Section IX .

group does not offer much steric hindrance. In other words the transition state comes earlier in the carbon-halogen bond formation reaction than for enols or enol esters.

The enolate differs from the enol in another important regard. Whereas the enol is a neutral species, the enolate being an anion is coordinated with its gegenion, existing as an ion-pair complex.[86]

The counter ion (cation) could affect the steric course of halogenation in two ways viz. (1) by shielding one side from attack or (2) by offering an anchoring to the halogenating reagent. At high dilutions and elevated temperatures the ion pair complex would be dissociated more than at low temperatures and high concentrations. A distinct temperature effect was observed in the halogenation of the lithium enolate of bromocamphor by t-butyl hypochlorite. At -100°C as much as 83 mole percent of product from exo entry of the reagent was formed, which probably indicates the effect of the cation on steric approach of the reagent.

However, the stereoelectronic preferance for exo approach of the reagent to the enolates is offset to a great extent when reagents such as sulfuryl chloride or the chlorine-2,6-lutidine adduct are used. Apparently carbon-halogen bond formation in the transition state of the halogenation of the enolate brings these reagents close enough to come within the sphere of steric interference from the C-8 methyl group and C-3 halogen substituent. Consequently these reagents are forced to form products with preferred endo entry.

V

THE EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

A. INTRODUCTION

The investigations on the course of halogenation of 3-mono-halogenocamphors were carried out using the P.M.R. properties of the epimeric 3-bromo-3-chlorocamphors in the mixture. In order to provide direct evidence for the correct assignment of spectral properties of these epimers and also to get an estimate of their relative stabilities it was desirable to isolate them in a state of high and known purity. Three lines of approach were undertaken in this regard, viz. (1) physical separation from a mixture of two epimers (2) selective decomposition of one of the epimers in the mixture and (3) stereoselective synthesis.

B. PHYSICAL SEPARATION

1. FRACTIONAL CRYSTALLISATION

Repeated crystallisation of the crude epimeric mixtures from methanol or petroleum ether at low temperatures led to epimeric mixtures free from other impurities, such as mono-halocamphors, but there was very little change, if any, in the ratio of the 3-bromo-3-chlorocamphors in successive recrystallisations. The mother liquors from the first few recrystallisations had usually an epimeric composition different from that in the crystals. As a preparative method it was totally unsuitable for the attain-

ment of the desired results.

2. CHROMATOGRAPHIC SEPARATION

The epimeric mixtures were eluted from neutral alumina columns with petroleum ether without any alteration in the epimer ratio. This treatment separates the monohalocamphors from dihalocamphors.

Thin layer chromatography on silica gel plates for camphor itself has been investigated.[87] Monohalocamphors and dihalocamphors have identical R_f using ethyl acetate-petroleum ether mixtures. With a benzene-petroleum ether-chloroform system better discrimination is observed, the R_f of dihalocamphors being greater than that of monohalocamphors. The mixture of epimeric chlorobromocamphors, however, appears as a single spot in both systems.

Vapour phase chromatography on a 1% DEGS column in an all glass equipment gave a single broad peak with the epimeric mixture. In other columns there is evidence of decomposition occurring.

C. SELECTIVE DECOMPOSITION

Reductive dehalogenation of α-haloketones is a well known reaction. In the cyclohexanone series selective preference has been demonstrated in the removal of bromine by hydrogen bromide. Lowry observed that the epimeric 3-bromo-3-chlorocamphors are debrominated either by zinc in acetic acid or potassium hydroxide in ethanol. It was considered likely that these dehalogenations might show a selectivity for the removal of bromine in a certain

orientation, presumably exo.*

A series of reagents was tried for effecting dehalogenation. In a general procedure a quantity of epimeric 3-bromo-3-chlorocamphor mixture free from other impurities was taken and the ratio of the two epimers determined by P.M.R. Dehalogenation was carried out to ~50% of the theoretical value for one halogen atom removal, either by using a limited amount of the reagent or by interrupting the reaction well before completion. The neutral products were extracted with petroleum ether, and the residue left after the removal of solvent was examined by P.M.R. The extent of dehalogenation was estimated from the relative areas of C-3 methine protons versus the C-4 proton. The signals from the methine proton also revealed whether debromination or dechlorination occurred. The ratios of epimeric 3-bromo-3-chlorocamphors was estimated from the integration of the C-4 proton signals appearing at 2.68 p.p.m. and 2.82 p.p.m. respectively for the two epimers in chloroform-d_1 solutions. Results are listed in Table X.

In all cases, except in the use of triphenylphosphine in methanol at low temperatures and high concentration and in alkyllithium compounds for prolonged periods, only debromination has been observed. Most of the dehalogenating agents did not show any observable difference in the rate of debromination of the two epimeric 3-bromo-3-chlorocamphors. These reagents are: alkoxides, iodide, thiourea, 2,6-lutidine, zinc in acetic acid, and tributyltin hydride. Only four reagents showed discrimination in the

* The reasons and justifications for this statement are given in section VI.

TABLE X

DEHALOGENATION OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

NO.	AMOUNT OF SUBSTRATE mg.	COMPOSITION % exo-BROMO EPIMER	REAGENT & CONDITIONS	NEUTRAL PRODUCT mg.	PRODUCT COMPOSITION %	COMPOSITION OF DIHALO-EPIMERS (% 3-exo-bromo)
1	348	78	NaI 1980 mg. in MeCOEt, 4 hrs., reflux	325	Monochloro 22.8 Chlorobromo 77.2	75
2	270	75	Thiourea 76 mg. EtOH Reflux, 18 hrs.	245	-	73.2
3	207	22	NaCN 31.3 mg. DMFA-H_2O 130°, 12 hrs.	149.3	Monochloro 70 Chlorobromo 30	8.6
4	267	38.6	Zinc 33 mg. ACOH Reflux	198	Monochloro 47.5 Chlorobromo 52.5	38.4
5	272	38	tri-n-BuSnH 150 mg. Et_2O (N_2) R.T., 1 hr.	310*	Monochloro 34.0 Chlorobromo 66.0	38.2
6	266	27.6	NaOMe-MeOH, 0.1M 5 ml. 120°, 10 hrs.	180**	Monochloro 9 Chlorobromo 91**	27.3
7	266	40	NaOtBu-t-BuOH, 0.1M 3 ml. 120°, 10 hrs.	172	Monochloro 8.3	37.5
8	266	27	---"--- 99°-100°, 1 hr.	255	Not estimated	26

TABLE X

DEHALOGENATION OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

NO.	AMOUNT OF SUBSTRATE mg.	COMPOSITION % exo-BROMO EPIMER	REAGENT & CONDITIONS	NEUTRAL PRODUCT mg.	PRODUCT COMPOSITION %	COMPOSITION OF DIHALO-EPIMERS (% 3-exo-bromo)
9	268	26	nBuLi 1.35 mmoles Pentane R.T. 15 min.	175	Monochloro 100	-
10	269	26	t-BuLi 0.66 mmoles Hexane R.T. 15 min.	230	Monochloro 41 Chlorobromo 59	28.6
11	270	73.3	t-BuLi 0.66 mmoles Hexane R.T. 150 min.	210	Monochloro 12.5 Monobromo 42.5 Chlorobromo 45	57.2
12	282	26	2,6-Lutidine 214 mg. Ethylene Glycol 155° 4 hrs.	230	Monochloro 58.5 Chlorobromo 41.5	26
13	278	50	PPh_3 255 mg. MeOH Reflux, 1 hr.	208.9	Monochloro 90 Chlorobromo 10	3
14	260	22	PPh_3 83.9 mg. MeOH Reflux, 1 hr.	236.9	Monochloro 30 Chlorobromo 70	11.3
15	267.2	22	PPh_3 88.8 mg. MeOH R.T., 10 hrs.	210	Monochloro 26 Chlorobromo 74	9.8
16	2142.0	45	PPh_3 741.2 mg. MeOH 0-4°, 12 hrs.	1951.0	Monochloro 41.7 Monobromo Chlorobromo 58.3	21.4

TABLE X

DEHALOGENATION OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

NO.	AMOUNT OF SUBSTRATE mg.	COMPOSITION % exo-BROMO EPIMER	REAGENT & CONDITIONS	NEUTRAL PRODUCT mg.	PRODUCT COMPOSITION %	COMPOSITION OF DIHALO-EPIMERS (% 3-exo-bromo)
17	536	65.5	PPh_3 212 mg. MeOH, -50^0	456	Monochloro 37.6 Monobromo	51.6
18	270	66	PPh_3 106 mg. t-BuOH 100^0	230	Monochloro 40 Chlorobromo 60	65
19	661	34	$NaBH_4$ 94.5 mg. MeOH-H_2O R.T. 30 min.	480	Not estimated	21.6

* The recovered oil contains an unidentified compound, presumably an organotin derivative.

** The proportion of monochlorocamphor is much less than expected. Halide ion estimation shows the extent of dehalogenation almost theoretical (equal to the amount of alkali present).

dehalogenation of the two epimers; these are: sodium cyanide at high temperatures in dimethyl formamide, alkyllithium compounds, sodium borohydride and triphenylphosphine in methanol. These reagents attack the 3-exo-bromo-3-endo-chloro epimer at a faster rate leaving behind larger proportions of 3-endo-bromo-3-exo-chlorocamphor than in the starting mixture. The largest amount of selectivity was observed in the reductive dehalogenation caused by triphenylphosphine. Thus it is possible to prepare 3-endo-bromo-3-exo-chlorocamphor in low yield from a mixture of the two epimers by selective dehalogenation with triphenylphosphine in a proton-donating solvent such as methanol.

D. STEREOSELECTIVE SYNTHESIS

Four possibilities were explored, viz. (1) halogenation of 3-halo-3-halomercuricamphors (ii) halodecarbonylations (iii) halodecarboxylations and (iv) stereoselective halogenation of 3-halocamphor enol acetates.

1. HALOGENATION OF 3-HALO-3-HALOMERCURICAMPHORS

3-Halomercuricamphors have been prepared[88] by the action of mercury^{II} halides on camphor in the presence of alkali. Using a similar procedure we attempted to prepare 3-bromo-3-iodomercury-camphor and 3-bromo-3-chloromercuricamphor from 3-endo-bromo-D-camphor. A white amorphous solid was isolated in low yields by the reaction with mercuric chloride. This decomposes above 200° and is insoluble in carbon tetrachloride, methylene chloride, benzene, chloroform, pyridine, nitromethane and dimethyl sulfoxide. Reaction with mineral acids gave 3-monobromocamphor and mercuric salts. On treating this material with chlorine in methylene chlor-

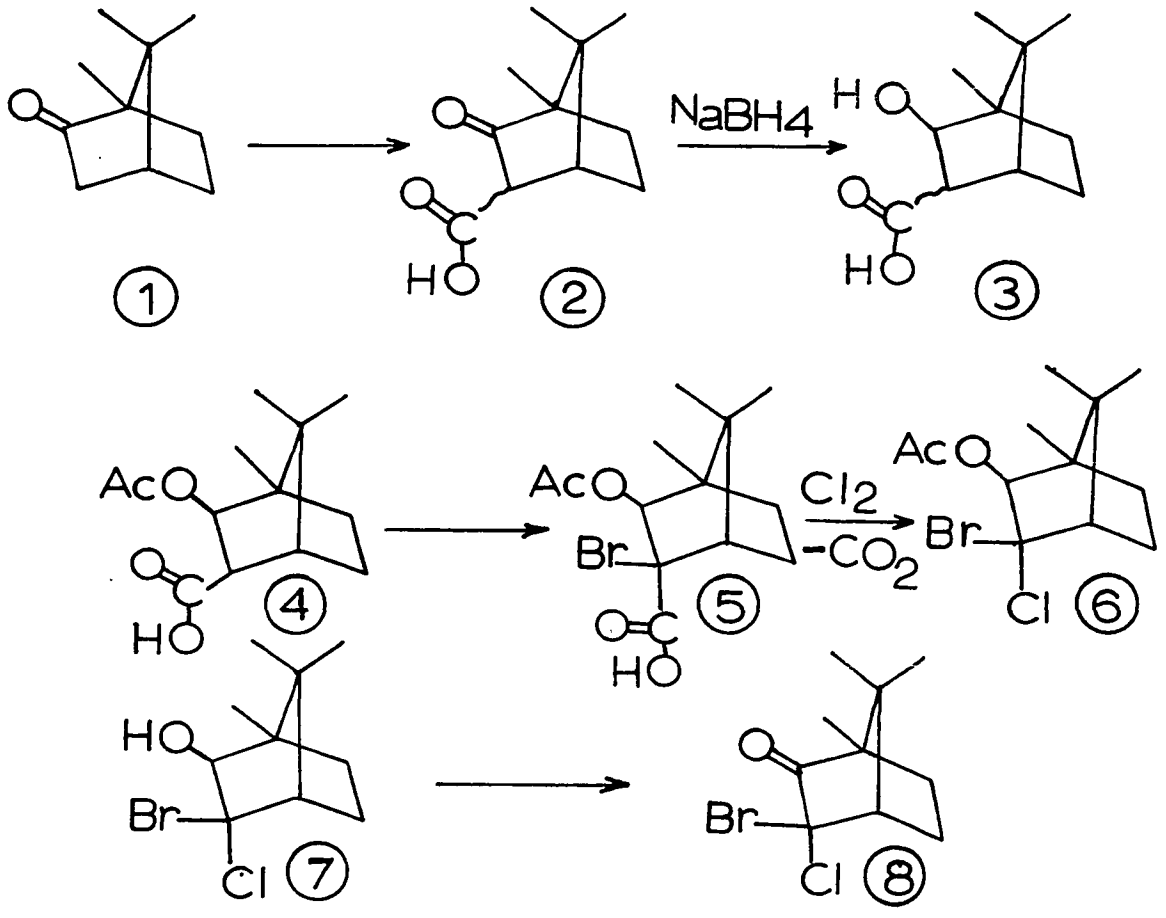
ide a mixture of epimeric 3-bromo-3-chlorocamphors was obtained with 3-exo-bromo-3-endo-chlorocamphor being 60 percent of the mixture.

2. HALODECARBONYLATIONS

3-Bromocamphor-3-carboxylic acid was prepared either from the carbonation of the magnesium enolate formed on treating 3,3-dibromocamphor with magnesium in ether, or from Hell-Volhard-Zelinsky bromination of camphor-3-carboxylic acid. The P.M.R. spectrum of this β-keto α-bromo acid shows only one multiplet centred around 175 c.p.s. arising from the C-4 proton, and on this basis this material was judged to be largely one single epimer. The bromo acid or its sodium salt decarboxylate readily (the free acid at its melting point) to 3-bromocamphor. When the acid chloride of the α-bromo acid was refluxed in carbon tetrachloride with a trace of pyridine, the neutral residue after work up showed in addition to 3-endo-bromocamphor an unidentified material and a small quantity of a material which on the basis of its P.M.R. signals (in the mixture) was judged to be a mixture of epimeric 3-bromo-3-chlorocamphors, in which the amount of 3-exo-bromo-3-endo-chlorocamphor is at least 85%. Repeated reactions with slightly larger amounts of pyridine resulted in the formation of a complex mixture without any trace of epimeric 3-bromo-3-chlorocamphors being present. When this neutral product was chromatographed over alumina a ketone was isolated which was judged to be a dimeric campho-ketene first reported by Staudinger, et al.[89] and shown to be mixture of two isomers by Baldwin, et al.[90]

3. HALODECARBOXYLATIONS

3-Bromocamphor-3-carboxylic acid, earlier found to be largely a single epimer from its P.M.R. spectrum was a possible starting material for preparing 3-exo-bromo-3-endo-chlorocamphor by halodecarboxylation, provided this last reaction was stereospecific. When the Kochi technique[91] of halodecarboxylation was used (calcium chloride, lead tetraacetate in benzene under nitrogen) on this α-bromo acid, 3-endo-bromocamphor was isolated as the major product. A small amount of epimeric 3-bromo-3-chlorocamphor mixture was detected by P.M.R. spectroscopy, the proportions of the two epimers being identical. Apparently, the carbonyl group at the β-position activates decarboxylation of the acid. In order to circumvent this difficulty the following scheme was devised:



The hydroxy acid (3) was characterised by infrared and P.M.R. spectroscopy. Acylation in acetic anhydride-pyridine at steam bath temperatures led to bornene-3-carboxylic acid[92], a known compound. Acetylation under milder conditions (10°, 4 hrs, room temperature, 12 hrs.) gave the expected acetoxy compounds (4). Hell-Volhard-Zelinsky bromination in glacial acetic acid was not successful; in refluxing chloroform-phosphorus tribromide reaction with bromine gave two products (a) a major neutral product and (b) an acid. The P.M.R. spectrum of the neutral product revealed it to be 3-bromo-2-acetoxy bornane which must have formed by decarboxylative bromination of the bornane carboxylic acid.* The acidic product had a structure consistent with the 2-acetoxy-3-bromo-bornane-3-carboxylic acid (5). Treatment of the silver salt of this α-bromo acid with chlorine gas in carbon tetrachloride gave a complex mixture containing at least five products by thin layer chromatography. This behaviour at the penultimate step necessitated the abandonment of the scheme.

4. HALOGENATION OF 3-HALOCAMPHOR ENOL ACETATES.

PREPARATION AND PROPERTIES OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS.

3-*exo*-Bromo-3-*endo*-chloro-D-camphor was prepared from 3-bromo-D-camphor enol acetate in one step. A solution of chlorine in carbon tetrachloride, the enol acetate in the same solvent and a crystal of iodine were stirred at room temperature. The only other product in the reaction is acetyl chloride. Pure 3-*exo*-bromo-3-*endo*-chloro-D-camphor is obtained in excellent yield and

* For a parallel case of halogenation by direct displacement of carboxyl group see reference 93.

is judged to be $\gg$99% epimerically pure by P.M.R. spectroscopy.

Identical treatment of 3-chloro-D-camphor enol acetate with bromine gave the epimeric 3-bromo-3-chlorocamphor in very good yields. The P.M.R. spectrum of this material reveals it to contain 93±1% of 3-endo-bromo-3-exo-chloro-D-camphor. Further purification has been achieved by selectively decomposing the other epimer with triphenylphosphine. A sample of such a material (i.e. 93±1% epimerically pure) after one treatment with triphenyl phosphine (50 percent of 1 equivalent of dehalogenation) and purification resulted in a product 95±1% epimerically pure. Further purification can be attained in theory but the yields would be low due to extensive decomposition.

The physical characteristics of the two epimers are given in table XI. Constants reported by Lowry are also given in the table for comparison. In order to get an estimate of purity of the product with which Lowry worked, the specific rotation, $[\alpha]_D$ offers the only reliable means of comparison, provided the values were obtained for pure epimers uncontaminated with other impurities. As many as twenty-six recrystallisations were used by Lowry, and the final figures of specific rotation reported by him are on samples which did not show any change in rotation on further crystallisations. These can then be taken as free of other contaminants. Using the method of optical superimposition, the molecular rotation of an epimeric 3-bromo-3-chlorocamphor should be the sum of the molecular rotation of D-camphor and the contributions by the two halogen substituents in the appropriate orientation. The calculated figures for these contributions

appear in section II (Table IV) and are based on specific rotations of 3-halocamphors obtained by us in chloroform solutions (Table III). Using these figures, and the molecular weight of the 3-bromo-3-chlorocamphors one obtains the specific rotation for 3-exo-bromo-3-endo-chloro-D-camphor, $[\alpha]_D = -4.5^\circ$ (calculated), and for 3-endo-bromo-3-exo-chloro-D-camphor, $[\alpha]_D = +100^\circ$ (calculated).

The epimer to which we assigned the structure of 3-exo-bromo-3-endo-chloro-D-camphor on the basis of its P.M.R. spectrum, and judged its purity ~100%, gave $[\alpha]_D^{19^\circ} = -4.6^\circ$ (c= 8.03, chloroform). The other epimer obtained in 95±1% purity from its P.M.R. spectrum gave $[\alpha]_D^{19^\circ} = +96.2$ (c= 8.01, chloroform). It is clear that the optical superimposition method predicts the correct direction of rotation for the two epimers. What is more satisfying is that the coincidence with the actually obtained specific rotation of 3-exo-bromo-3-endo-chloro-D-camphor is remarkable.

Assuming that the calculated figures for the optical rotation of the two epimers are also the actual figures for the pure epimers one can calculate the approximate purity of the epimers which Lowry obtained. The epimer for which Lowry obtained $[\alpha]_D = +10^\circ$ (c= 10, chloroform) is then 3-exo-bromo-3-endo-chloro-D-camphor of 86.1% epimeric purity, and the epimer for which he reported $[\alpha]_D = 64^\circ$ (c= 10, chloroform) is 3-endo-bromo-3-exo-chlorocamphor of 65.5% epimeric purity.

E. RELATIVE STABILITIES OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

1. GENERAL CONSIDERATIONS

In the first chapter it was pointed out that the ground state energies of epimeric α-haloketones need not be identical. Factors that govern ground state stabilities of α-halocyclohexanones were outlined earlier. These will now be considered for epimeric 3-bromo-3-chlorocamphors. There are two classes of influences which can affect the relative energies of the two epimers, viz. steric factors and electronic factors.

The obvious steric factors in the bornane skeleton arise from the interactions between the C-8 methyl group and the 3-exo substituents in the skeleton. There are several independent pieces of information which indicate that such an interaction does in fact exist which causes the endo epimers to be thermodynamically more stable than the exo epimer. For example isoborneol (2-exo-bornanol) is less stable than borneol (2-endo-bornanol). On the other hand when the C-8 methyl group is not present exo substituents are more favoured. isonorBorneol (2-exo-norbornanol) is more stable than norborneol (2-endo-norbornanol)indicating that the C-8 methyl group affects stability of these compounds. In camphor the 3-endo-substituted epimers are favoured; for instance 3-endo-bromocamphor is 1.44 kcals/mole more stable than 3-exo bromocamphor, indicating that the interaction between exo bromine and the C-8 methyl group must be repulsive.

Comparison of the steric interactions between the C-8 methyl and exo bromine on the one hand and C-8 methyl and exo chlorine on the other hand from Dreiding models indicates that these inter-

TABLE XI

Compound	1 mp,°	2 $[\alpha]_D^{CHCl_3}$, °	3 $\nu_{max(CS_2)}^{C=O}$ cm^{-1}	4 P.M.R. Signals δ p.p.m.	5 Purity %	6 mp,°	7 $[\alpha]_D^{CHCl_3}$, °	8 Purity %
3-exo-Bromo-3-endo-Chloro-D-Camphor	64-64.5	-4.6 (C = 8.03, 19°)	1768	C_4H:2.82 Me C-8 1.25 C-9 1.11 C-10 1.00	≳99 (P.M.R.) ~100 ($[\alpha]_D$)	61	+10 (C = 10)	86.1
3-endo-Bromo-3-exo-Chloro-D-Camphor	50-50.5	+96.2 (C = 8.01, 19°) (+100 for 100% pure material)	1768	C_4H:2.68 Me C-8 } 1.13 C-9 } C-10 1.03	95±1 (P.M.R.)	55	+64 (C = 10)	65.5

Columns 6 and 7: Values reported by Lowry[36].

actions are certainly greater in the former case. One therefore expects the epimer with exo bromine to be less stable than the one with exo chlorine. This approximation ignores the interaction between 3-endo halogen and the C-5 and C-6 endo hydrogens.

There is an electronic factor also involved with its origin in dipole-dipole repulsion between the α-halogen and the carbonyl oxygen. All available information on 3-halocamphors points to the fact that the σ - plane of the carbonyl group bisects the angle between the two substituents at C-3. The dipole-dipole repulsions between bromine-oxygen and chlorine-oxygen will therefore cancel out in both the epimeric 3-bromo-3-chlorocamphors. One would therefore predict that the C-8 methyl-C-3 halogen interaction would be the determining factor in the relative stabilities of the two epimers. As stated before this would tend to make the 3-exo-bromo-3-endo-chlorocamphor less stable than the other epimer. A complete information regarding these interactions in the epimeric 3-bromo-3-chlorocamphors is not available and hence their relative stabilities could not be computed. Attempts were made to obtain this information from measurements of the equilibrium constant which can be evaluated either by attaining an equilibrium between the two epimers in a reversible process or by kinetic measurements.

2. ATTEMPTED EQUILIBRATION

(a) With hydrogen bromide

A solution of 3-exo-bromo-3-endo-chlorocamphor in carbon tetrachloride saturated with dry hydrogen bromide did not show any sign of epimerisation after 24 hours at room temperature. The

same substrate in a mixture of acetic acid and chloroform -d_1 saturated with dry hydrogen bromide formed considerable 3-chlorocamphor after 72 hours at room temperature although there was no sign of epimerisation. A control experiment with a solution of 3,3-dibromocamphor in acetic acid saturated with hydrogen bromide after heating at $\sim 100^{\circ}$ for 12 hours gave a quantitative yield of 3-bromocamphor. Apparently the liberated bromine was all consumed by the solvent acetic acid.

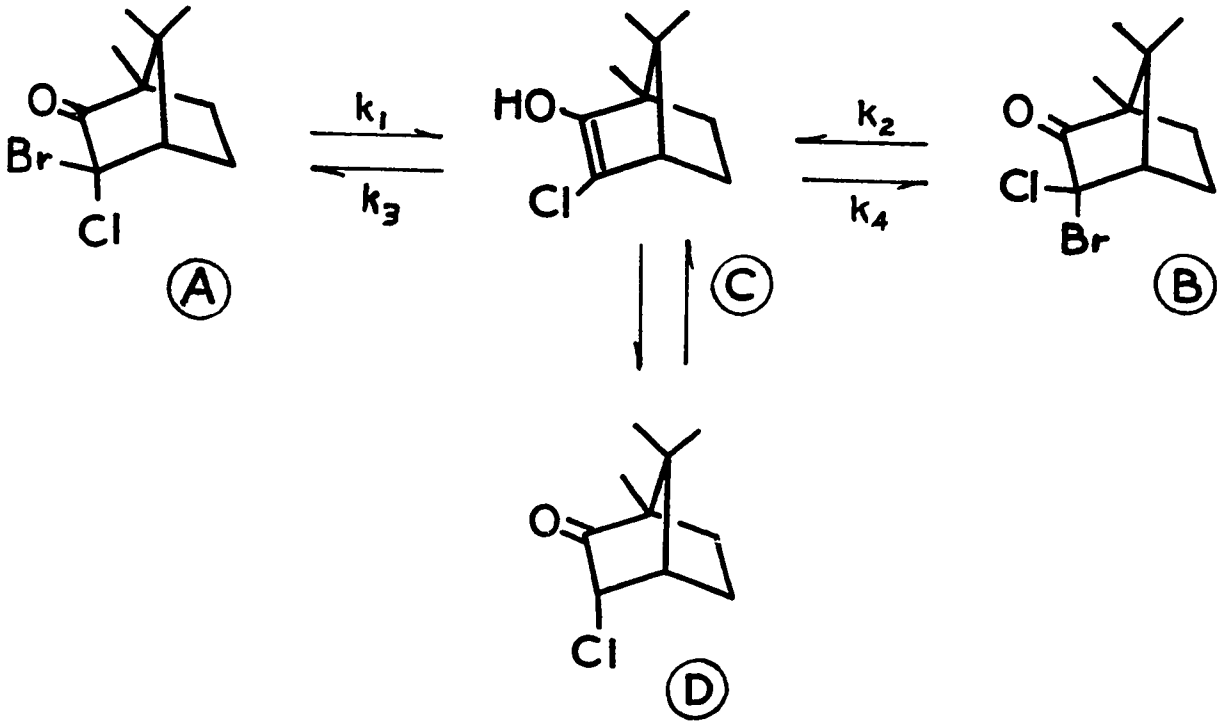
At elevated temperatures ($\sim 100^{\circ}$) in trifluoroacetic acid saturated with hydrogen bromide 3-exo-bromo-3-endo-chlorocamphor formed about 15% of 3-chlorocamphor after 50 hours whereas 3-endo-bromo-3-exo-chlorocamphor formed about 8% of 3-chlorocamphor in 100 hours. In neither case was there any evidence for epimerisation. Free bromine was detected in both of these cases.

(b) With Triphenylphosphine

In benzene, carbon disulfide or acetonitrile solutions triphenylphosphine did not epimerise 3-exo-bromo-3-endo-chlorocamphor at room temperature. At elevated temperatures in benzene 3-chlorocamphor enolphosphonium bromide was formed. In acetonitrile at elevated temperatures 3-endo-chlorocamphor formed. There was no sign of epimerisation.

3. KINETIC APPROACH

If the relative rates of debromination of the two epimeric 3-bromo-3-chlorocamphors are known accurately, and the rate of formation of the two epimers in the bromination of the chlorocamphor are also known accurately in the same system at the same temperature, one can set up a hypothetical equilibrium as follows:



This assumption is valid only when the bromination and debromination reactions approach the condition of being the microscopic reverse of each other. Using this approach, the stabilities of the two epimers have been evaluated in two systems.

A. In acetic acid-bromine-hydrogen bromide system

At 110° bromination of 3-endo-chlorocamphor by bromine in acetic acid for one hour in the presence of catalytic amounts of hydrogen bromide gave 39.3 percent of 3-exo-bromo-3-endo-chlorocamphor and 60.7 percent of 3-endo-bromo-3-exo-chlorocamphor. Hence for this system,

$$k_4/k_3 = 1.54 \qquad (1)$$

The relative rates of debromination of the two epimeric 3-bromo-3-chlorocamphors were estimated by a competitive debromination technique

in acetic acid saturated with hydrogen bromide at 110° for ten hours. The relative rates of debromination were

$$k_1/k_2 = 2.2 \qquad (2)$$

The equilibrium constant $K = \frac{B}{A}$, where the brackets denote concentrations.

$$K = \frac{k_1 k_4}{k_2 k_3} \qquad (3)$$

Using the experimental values of k_1/k_2 and k_4/k_3,

$$K = 3.4 \qquad (4)$$

From the relation $\Delta F = -2.3\ RT \log K$, $\Delta F = -0.935$ Kcal/mole at 110° in acetic acid. This gives 23 percent of 3-exo-bromo-3-endo-chlorocamphor and 77 percent of 3-endo-bromo-3-exo-chlorocamphor in this system of equilibrium.

B. In aqueous acetonitrile

The relative rates of formation of the two epimeric 3-bromo-3-chlorocamphors, $k_4/k_3 = 4$, at 25° in 75 percent acetonitrile-25 percent water-potassium acetate-bromine system.

The rates of debromination were computed from the reductive debromination of the two epimeric dihalocamphors by triphenylphosphine in 75 percent acetonitrile-25 percent water-potassium acetate system at 25°. This reaction is assumed to involve the enol of chlorocamphor as intermediate (see section VI), and as a first approximation is assumed to be microscopic reverse of the bromination reaction in acetonitrile system. The relative rates of debromination, $k_1/k_2 = 4$ at 25°.

The use of these relative rate constants gave K = 16; ΔF = -1.645 Kcal/mole at 25° in favour of 3-endo-bromo-3-exo-chlorocamphor.

VI

REDUCTIVE DEHALOGENATION OF 3,3-DIHALOCAMPHORS

KINETICS AND MECHANISM

A. INTRODUCTION

Reductive dehalogenation of α-haloketones results in the replacement of an α-halogen atom by a hydrogen atom. Hydrogen halides can cause this reaction, presumably either by protonation of carbonyl oxygen followed by attack of halide ion in a S_N2 fashion on the α-halogen, or by a six-centred mechanism.[94]

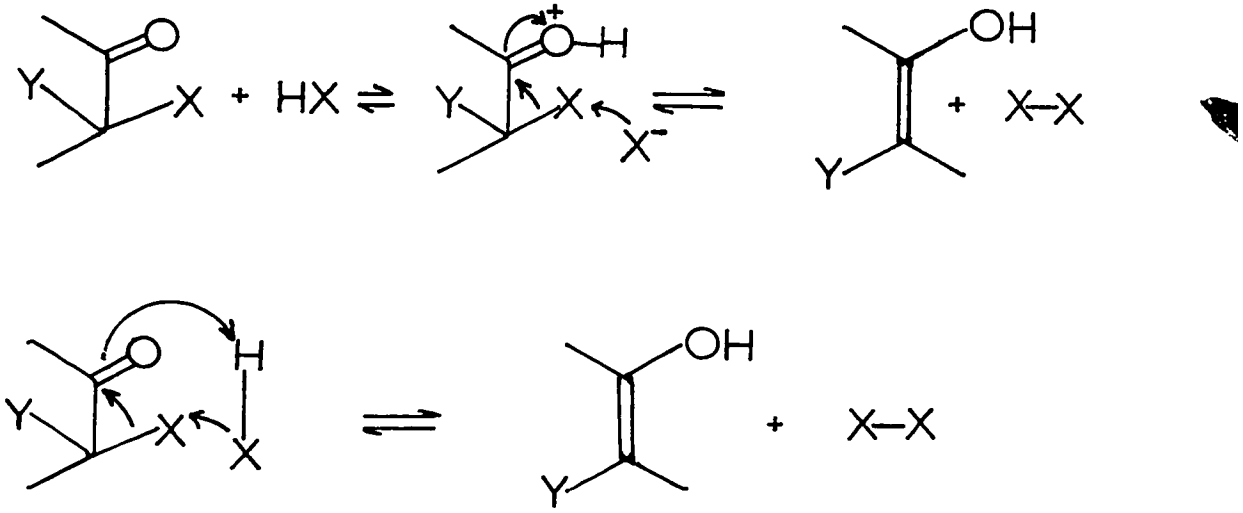


Fig. 11.

In either case the resulting intermediates are the enol of the dehalogenated ketone and a molecule of halogen. If the halogen can be removed from the system by a suitable trapping agent, e.g. 2-naphthol, the dehalogenated ketone can be isolated. In the absence of a trapping agent the enol can be rehalogenated. This process can be repeated several times till finally an equilibrium mixture of haloketones is formed. The significance of this process was outlined in section I. In as much as dehalogenation by hydrogen halides is the microscopic reverse of acid catalysed halogenation of ketones involving an enol intermediate, the electronic requirement of p-orbital overlap in the transition state for dehalogenation ought to be the same as for halogenation. In the chair form of cyclohexanone derivatives axial preference for halogen entry exists in halogenation. Dehalogenation in a microscopically reverse process ought to exhibit preference for axial halogen removal. There is selectivity in the removal of bromine in two orientations in hydrogen halide dehalogenation of chlorobromocholestanones.[12] Another feature that has been observed in this system is that under experimental conditions debromination occurs in preference to dechlorination, a fact which has been explained on the basis of relative bond strengths of the two types of carbon-halogen bonds.

Several other reagents are known to cause reductive dehalogenation. A partial list of such reagents is to be found in Table X , section V. In general the reagents causing reductive dehalogenation are nucleophilic in nature. These are quite often assisted, as in the case of bromide anion, by proton catalysis.

For the complete stoichiometry of the reaction a proton source is required which is usually provided by the solvent. Reductive dehalogenation of α-haloketones causes oxidation of the reagent. In this sense α-haloketones may be considered as either positive halogen compounds or as oxidising agents.

Very little information exists in the literature regarding the mechanism and stereoelectronic requirements of the reductive dehalogenation of α-haloketones, although these reactions have either found synthetic use or accompany certain preparative procedures.

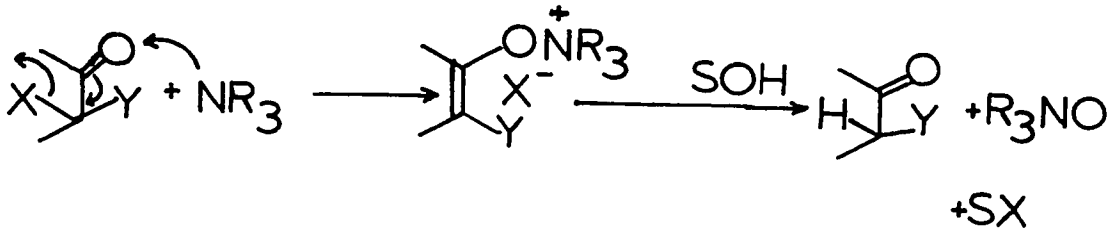
In recent years the interest in this class of compounds has been renewed in relation to the mechanistic problems concerning nucleophilicity. Mechanistically an α-haloketone is a polydentate electrophile, i.e. it has several electrophilic centres where a nucleophile can attack. According to Chopard[95] these centres are: the oxygen atom, the carbonyl carbon, the α-carbon, the α-halogen and the α-hydrogen. Nucleophilic attack on the first four centres* can cause reductive dehalogenation.

Nucleophilic attack on α-hydrogen leads to the enolate of an α-haloketone. This process competes with reductive dehalogenation which can occur by attack on the rest of the electro-

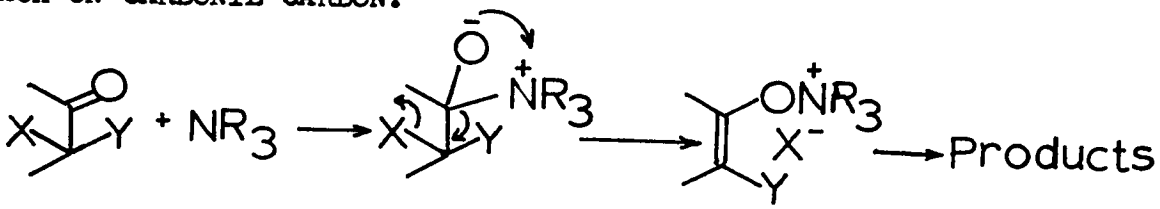
* Reductive dehalogenation from attack on oxygen, carbonyl carbon and α-halogen are authenticated. Attack on α-carbon, for example by trialkylphosphines gives an α-ketophosphonium salt which is normally stable to the reaction condition. On boiling with dilute alkali this is cleaved to dehalogenated ketone and triphenylphosphine oxide.[96] The resulting product provides a basis for considering the α-carbon also as a site of attack leading to reductive dehalogenation.

philic centres. A generalised scheme of reductive dehalogenation proceeding from each of these centres is shown below:

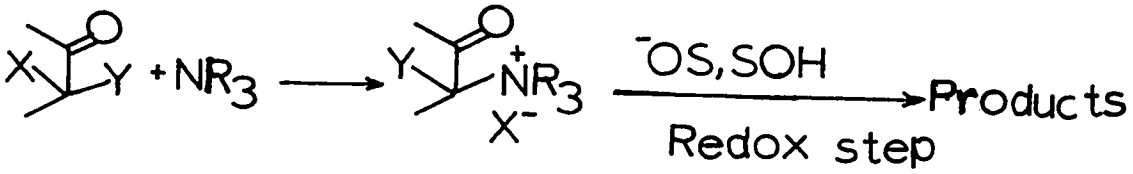
ATTACK ON OXYGEN.



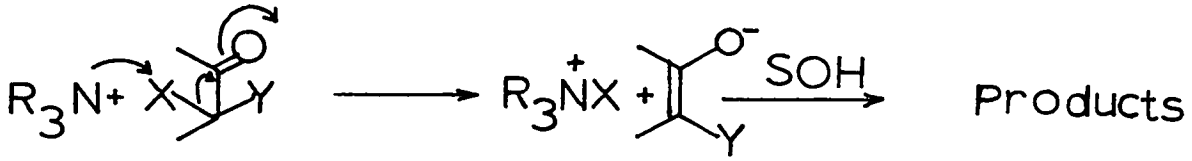
ATTACK ON CARBONYL CARBON.



ATTACK ON α-CARBON.



ATTACK ON α-HALOGEN.



The factors which cause preferential attack at one or the other site are complex. A precise understanding of these is lacking at present. In recent years Pearson[97] has developed the concept of hard and soft acids and bases (HSAB) for explaining the reactivity of nucleophiles (Lewis bases) towards electrophilic centres (Lewis acids). There is a mutual affinity between

hard bases and hard acids; similarly soft bases prefer soft acids.[98] Hardness is associated with high ionic character between the acid-base bond. Factors favouring hardness are small atomic radius, high effective nuclear charge, low polarizability and low ease of oxidation. The proton is a hard acid. Bases containing fluorine, oxygen or nitrogen as donor atomsare hard. Softness is associated with covalent character in acid-base bond. Halogen atoms, sp^3 carbon, O^{II} and S^{II} are soft acids. Iodide and phosphines are soft bases. According to Pearson[97(c)] the hydrogen and the carbonyl carbon in an α-haloketone are hard acid centres. The α-carbon is a medium hard acid, the oxygen and halogen atoms are soft acid centres.

3,3-Dihalocamphors are comparatively simple systems, and are good model compounds for studying the mechanism of reductive dehalogenation. An S_N2 attack on C-3 would require a linear arrangement of the attacking nucleophile, the C-3 centre and the departing group. The presence of C-8 methyl group would cause such a transition state to be extremely crowded and energetically highly unfavourable. This leaves three potential centres of nucleophilic attack which for brevity will be named as "O-route", "C-2 route" and "X-route" for reductive dehalogenation.

Five representative classes of reagents were chosen for the present study which have earlier been shown (SectionV) to cause reductive dehalogenation of 3,3-dihalocamphors. Investigations on these reagents involved use of 3,3-dibromocamphor, 3-exo-bromo-3-endo-chlorocamphor and 3-endo-bromo-3-exo-chlorocamphor. The first two were $\sim$ 100% pure, the last one 95 $\pm$ 1% pure. In

addition to the attempted elucidation of mechanism of reductive dehalogenation, particular interest centred around selectivity in the dehalogenation of the two epimeric chlorobromocamphors.

B. DEHALOGENATION BY TRIPHENYLPHOSPHINE

1. IN METHANOL

3-endo-Bromocamphor and 3,3-dichlorocamphor were inert to triphenylphosphine in refluxing methanol whereas 3,3-dibromocamphor gave quantitative yields of 3-endo-bromocamphor even below -70°. The epimeric 3-bromo-3-chlorocamphors gave 3-endo-chlorocamphor under kinetic conditions.

The rates of dehalogenation of 3,3-dihalocamphors were measured by following the disappearance of triphenylphosphine, between 15° and -45°. Initial concentrations in the halocamphor and triphenylphosphine were kept identical and the data were processed for a second order reaction from the expression[99]

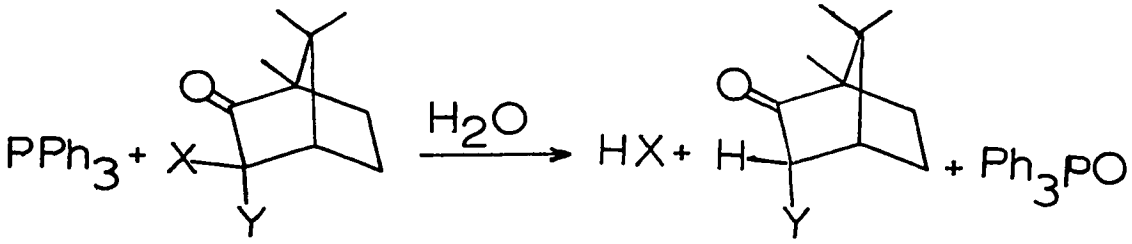
$$k_2 t = \left[\frac{1}{C} - \frac{1}{Co}\right]$$

where Co was the concentration of the substrate and the reagent in the beginning and C was the concentration of triphenylphosphine at time t.

The second order plots were not linear between -5° to 15° but became reasonably linear below -5° for over 50% of the reaction. The relative rates of debromination of the dihalocamphors were in the order: 3,3-dibromocamphor > 3-exo-bromo-3-endo-chlorocamphor > 3-endo-bromo-3-exo-chlorocamphor. (See Plate 11).

2. IN 75% ACETONITRILE-25% WATER

Acetonitrile was chosen as an inert co-solvent since it has been used in the studies on dehalogenation of α,α-dihalo amides by triphenylphosphine[100] and α-haloketones by trialkyl phosphites.[101] The solvent system consisted of 75 parts of acetonitrile, 25 parts of water by volume and contained 0.01M potassium acetate buffer. In this system the reaction between 3,3-dibromocamphor and triphenylphosphine was followed at 25° both by a modified Volhard estimation of halide ions and by the iodometric determination of the disappearance of triphenylphosphine. Exactly one equivalent of halide ion was liberated for each mole of triphenylphosphine consumed, the relationship being maintained for over 80% of the reaction. Product analysis after about 99% of the reaction gave 97% of 3-endo-bromocamphor of at least 98% epimeric purity. Under these conditions the 3-bromo-3-chlorocamphor gave 3-endo-chlorocamphor of at least 98% epimeric purity in quantitative yields. The overall stoichiometry of the reaction thus was:



X = Br, Y = Br or Cl.

As in the case of the methanol system, 3-endo-bromocamphor and 3,3-dichlorocamphor remained inert towards triphenylphosphine in this solvent system also.

The rates of debromination of the two epimeric 3-bromo-3-chlorocamphors were measured at 25°, 35°, 45° and 55°, while that

of 3,3-dibromocamphor was measured at 15°, 25°, 35° and 45° as a function of the disappearance of triphenylphosphine. The data were processed for a second order reaction from the expression[99]

$$k_2 t = \frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)} ,$$

where a and b are initial concentrations of triphenylphosphine and the halocamphor respectively, and x is the fraction of reaction after time t. The data gave an excellent fit to the second order kinetic equation above, the variation in the calculated value of the second order rate constant k_2 being ±2%. At 25° the numerical value of the rate constant k_2 was 27.3, 6.73 and 1.65 litres $mole^{-1}$ min^{-1} for 3,3-dibromocamphor, 3-exo-bromo-3-endo-chlorocamphor and 3-endo-bromo-3-exo-chlorocamphor respectively. The relative rates were 16:4:1 in that order. (Plate 12).

The Arrhenius plots for these three dihalocamphors were linear in the range 15° to 55° (Plate 13). The Arrhenius parameters are summarised below:

Substrate	E_A kcal/mole	$\Delta H^{\#}$ kcal/mole
3,3-Dibromocamphor	9.6	9.0
3-exo-Bromo-3-endo-chlorocamphor	9.5	8.9
3-endo-Bromo-3-exo-chlorocamphor	9.5	8.9

3. EFFECT OF SOLVENTS ON RATES

The rate of debromination of 3,3-dibromocamphor was measured at 25° in five aqueous solvents bufferred with potassium acetate. The second order rate constants k_2 varied between 0.84 in 80%

dioxane to 559 litres $mole^{-1}$ min^{-1} in aqueous methanol. The log k_2 were plotted against the Winstein Y values for these solvents.[102] The log k_2 increased with the increase in the Y value of the solvents (80% dioxane, 80% acetone, 80% ethanol and 80% methanol in that order), but the value of k_2 in 4M acetic acid (Y = -0.4) was greater than in 80% ethanol (Y = 0.0) and presumably reflects the greater proton donating ability of acetic acid system. (Plate 14).

4. IN APROTIC SOLVENTS

In anhydrous benzene the reaction between 3,3-dibromocamphor and triphenylphosphine at $\sim$ 100° gave a crystalline salt. The P.M.R. spectrum of this material in benzene was consistent with the structure of 3-bromocamphor enol phosphonium bromide, and had the quaternary methyl groups of the bornane skeleton centred at 1.03, 0.80 and 0.68 p.p.m. There was a one proton signal (multiplet) at 2.47 p.p.m. with a primary coupling of $\sim$ 5 c.p.s. and a secondary coupling of $\sim$ 1 c.p.s. The position as well as the coupling pattern of this signal matched the allylic (C-4) proton in 3-bromocamphor enol acetate (Plate 9). This salt was very hygroscopic and in contact with moisture gave 3-endo-bromocamphor, triphenylphosphine oxide and hydrogen bromide.

5. DISCUSSION

An outstanding feature of the reductive dehalogenation of epimeric 3-bromo-3-chlorocamphors by triphenylphosphine in proton donating media was a marked selectivity in the removal of exo bromine in preference to endo bromine. The order of selectivity was a factor of 4 at 25° for these two orientations.

A study of halogenation of 3-halocamphors made earlier led to the conclusion that in camphor molecule the stereoelectronic factor in halogenation favours the exo approach of the reagent. The microscopic reverse of this process, viz. reductive dehalogenation, should also favour the removal of exo-substituent. The selectivity observed in the removal of exo bromine in the present case is strongly suggestive that the process is under the control of the same stereoelectronic factors which operate in the halogenation reactions involving enol or enolates of 3-halocamphors. The steric factor is seemingly subordinated.

If this interpretation is correct, then one would predict that the transition state for dehalogenation in the present case must lead to the enol or enolate of monohalocamphors. The evidence obtained in the present studies offers support for this contention. In analogy to the halogenation reactions one would expect the protonation of enol or enolate to occur predominantly or perhaps exclusively from the exo direction, giving 3-endo-halocamphor in the kinetically controlled product. It will be recalled that the equilibrium mixture of 3-monohalocamphors contains at least 10% of the exo epimer. Dehalogenation of dihalocamphors by triphenylphosphine gave at least 98% of 3-endo-halocamphors which would seem to support the intermediacy of enol or enolate in the reductive dehalogenation.

The product analysis, stoichiometry and kinetic data in this remarkably clean reductive dehalogenation prompted us to make some speculations regarding the mechanism of this reaction. In the beginning of this chapter it was suggested that the attack of the

nucleophile can occur at three positions in the dihalocamphor ultimately leading to reductive dehalogenation. These three modes were termed the "O" route, the "C_2" route and the "X" route. A second order rate dependence and a marked increase in rate with increasing polarity of the solvent medium indicate that the rate determining step is bimolecular and involves a polar transition state since the reactants are neutral. All the three modes of dehalogenation would be consistent with this observation. There seems to be a distinct enhancement of rate with increasing hydrogen ion concentration, a factor which outweighs the solvent polarity in the case of acetic acid medium. This suggests the role of proton catalysis. When considered along with the earlier inference that the enol or enolate of monohalocamphor is probably an intermediate, the balance of evidence would seem to favour an attack on bromine, the transition state directly leading to an enol of halocamphor and phosphonium bromide. The 'X' route has been suggested in the dehalogenation of α-haloketones by triphenylphosphine in recent years by several workers.[100,103-105]

C. DEHALOGENATION BY ALKOXIDES

1. POTASSIUM METHOXIDE IN METHANOL

The reaction of 3,3-dibromocamphor with potassium methoxide in methanol at 25° was not a clean reductive dehalogenation. From the products formaldehyde was isolated and identified as its 2,4-dinitrophenylhydrazone, and presumably arose from the oxidation of methanol at some stage of the reaction. There was no trace of 3-bromocamphor in the products.

In a quantitative study nearly two equivalents of halide ions were observed to have been liberated for one mole of the reacted substrate (3,3-dibromocamphor). The reaction was found to be too complex to warrant detailed investigations.

2. POTASSIUM ISOPROPOXIDE IN 2-PROPANOL

The reaction of 3,3-dibromocamphor with potassium isopropoxide in 2-propanol at 100° gave 3-monobromocamphor and acetone (recovered as 2,4-dinitrophenylhydrazone). When the reaction was carried out at 25° it was found that the solvent, 2-propanol, itself reacted slowly with the dihaloketone even under neutral conditions to give a product which was judged to be diisopropyl ketal of camphane 2,3-dione from its P.M.R. spectrum and reactions.*

Relative rates of dehalogenation of 3-bromo-3-chlorocamphors and 3,3-dibromocamphor were measured using a competitive dehalogenation technique (see Experimental section). The rates were measured at 25° and the product identification established that only debromination occurred.

* 3,3-Dibromocamphor solutions in 2-propanol turned yellow soon after preparation at room temperature and gave acid titres corresponding to 32% of hydrogen bromide per mole of haloketone in12 hours at 25°. In 60 hours this titre rose to 100%. The epimeric 3-bromo-3-chlorocamphors liberated less than 6% hydrogen halide per mole in 100 hours. Controls with t-butyl alcohol and methanol did not give any dehalogenation of 3,3-dibromocamphor. Quantitative analysis showed that 2 equivalents of hydrogen halide were liberated for each mole of the haloketone. A neutral petroleum ether soluble product was isolated in these reactions as an acrid smelling oil after chromatography over alumina. Attempted distillation gave camphor quinone identified by P.M.R. and V.P.C. The infrared and P.M.R. spectrum of this oil were consistent with the structure of camphane-2,3-dione-diisopropyl ketal. The isopropoxy groups were identified by decoupling experiments. It is not certain whether the ketal is at C-2 or C-3.

3,3-Dibromocamphor	k (relative) = 2.5
3-exo-Bromo-3-endo-chlorocamphor	k (relative) = 1.06
3-endo-Bromo-3-exo-chlorocamphor	k (relative) = 1.00

3. POTASSIUM t-BUTOXIDE IN t-BUTYL ALCOHOL

The reaction of this reagent with 3,3-dibromocamphor at 25° gave 3-monobromocamphor in the neutral products, accounting for 34.5% of the starting material. The aqueous extracts in the work up contained acetone (isolated as its 2,4-dinitrophenylhydrazone) presumably arising from oxidative decomposition of t-butyl alcohol and considerable quantity of a bromoacid of undetermined structure.

4. DISCUSSION

The reaction of 3,3-dihalocamphors with alkoxides is complicated and is dependent on the nature of the alkoxide and the temperature of the reaction. At least some of the alkoxide (or the alcohol) seems to get oxidised to a carbonyl compound. The reaction of methoxide and t-butoxide also gave acidic products which could have arisen by the cleavage of the camphor skeleton involving an attack of the alkoxide on the carbonyl oxygen (C-2 attack). In one case where reasonably clean dehalogenation could be demonstrated (i.e. isopropoxide in 2-propanol) there was no appreciable selectivity in the debromination from exo and endo orientations of bromine.

D. DEHALOGENATION BY SODIUM BOROHYDRIDE

1. PRODUCTS AND RATES

The reaction of 3,3-dibromocamphor with sodium borohydride in

2-propanol at 25° gave largely 3-monobromocamphor and some bromohydrin identified by P.M.R. spectroscopy in the neutral products after work up. Under these conditions 3-endo-bromocamphor was inert to the reagent.

Preliminary investigations showed that the reaction is not first or second order.

A competitive reaction technique gave the relative rates of decomposition of 3-exo-bromo-3-endo-chlorocamphor and 3-endo-bromo-3-exo-chlorocamphor in the ratio of 2:1, respectively, in 2-propanol solutions at 25°.

In an attempt to decide whether a bromohydrin could be an intermediate in the reductive dehalogenation of the dihalocamphors it was found that the crude dibromohydrin prepared by the reduction of 3,3-dibromocamphor with lithium aluminium hydride was not debrominated under the conditions of the kinetic estimations.

2. DISCUSSION

Reductive dehalogenation of α-bromopinocamphanone by sodium borohydride has been observed.[106] These authors had suggested that a bromohydrin could be an intermediate in this reaction. We did not find any positive evidence to support this view. Since the bromohydrin obtained by the reduction* of 3,3-dibromocamphor

* Reduction of 3,3-dibromocamphor by lithium aluminium hydride in ether gave a mixture of mono and dihalohydrins. Reduction of 3-endo-bromocamphor with lithium aluminium hydride in ether at reflux temperatures gave ~85% of 2-endo-bornanol and a minor product (presumably 2-exo-bornanol). With a limited quantity of the hydride reagent at ~0° in ether a bromohydrin was obtained. The P.M.R. spectrum of this bromohydrin had a one proton singlet at 2.25 p.p.m. (OH), a one proton quartet at 3.79 p.p.m. (CHOH), and a one proton multiplet at 4.79 p.p.m. (CHBr). The methyl

was stable to sodium borohydride under kinetic conditions, it is likely that the reductive debromination might be occurring through an 'X' route. There was some selectivity in this dehalogenation, the exo bromine being removed twice as fast as the endo bromine.

E. DEHALOGENATION BY TERTIARY AMINES

1. N-METHYLPIPERIDINE

At 135°, excess N-methylpiperidine cleanly debrominated 3,3-dibromocamphor completely in a few minutes. Exactly one equivalent of halide ion was liberated. The petroleum ether soluble products contained 3-monobromocamphor (~95%) and a small quantity of an unidentified polar material (~5%). A deep yellow brown viscous mass, insoluble in petroleum ether, soluble in dilute mineral acids, was formed and is presumably derived from oxidative polymerisation of the base. 3-endo-Bromocamphor is unaffected by N-methylpiperidine at this temperature even after 24 hours.

A N-methylpiperidine solution of 3,3-dibromocamphor started reacting at ~ 25° within a few hours. A white crystalline mass settled down first. In about 24 hours this began turning yellow.

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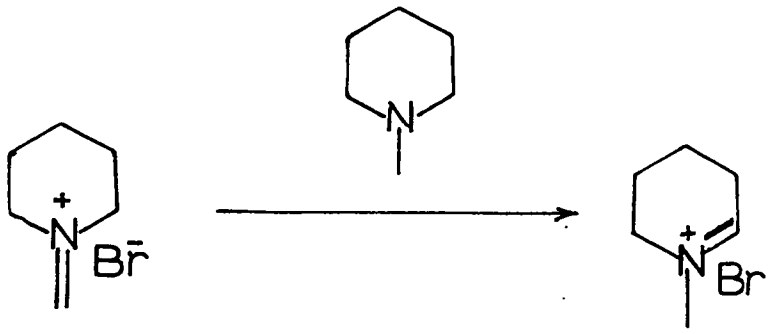
signals appeared as singlets at 0.98, 0.96 and 0.91 p.p.m. The 3.79 p.p.m. signal had a primary coupling of 9 c.p.s. and a secondary coupling of 2 c.p.s. The former was a cis vicinal coupling and the latter a long range coupling. This latter requires the orientation of the C-2 methine proton to be exo in order to couple with the C-6 exo proton. On treatment with W_4-Raney nickel in ethanol at room temperature the bromohydrin smoothly passed into 2-endo-bornanol. On the basis of this evidence we assign the structure of 3-endo-bromo-2-endo-bornanol to this bromohydrin. This same compound from reduction of 3-endo-bromocamphor was erroneously reported as 3-endo-bromo-3-exo-bornanol by W.Z. Antkowiak[107] recently. (See PLATE 8).

A small quantity of the white crystals was isolated and was shown to be a quaternary ammonium bromide. The P.M.R. spectrum of the crystalline material in chloroform-d_1 showed a two proton singlet centred at 8.67 p.p.m., a four proton multiplet centred at 3.25 p.p.m. and a broad band centred at 1.91 p.p.m. with relative area corresponding to six protons. From halide ion titre the molecular weight (allowing one bromide ion per mole) was calculated to be 177.5. Reduction with sodium borohydride in methanol gave N-methylpiperidine. These data fit the structure A. On remaining in contact with excess N-methylpiperidine the yellowish material is formed. Its P.M.R. spectrum is consistent with B, or an enamine from B.



A B

The yellow colour is probably due to polymerisation-condensation of B with excess base. In contrast to the high temperature reactions, at low temperatures 3-monobromocamphor is not detected. Relative rates of reductive dehalogenation of the epimeric 3-bromo-3-chlorocamphors were estimated by a competitive reaction (see Experimental) at 140°. An average of two

independent runs showed no difference in the relative rate of debromination of the two epimers.

2. PYRIDINE

3,3-Dibromocamphor in excess pyridine at 135° for 50 hours gave 10% of 3-bromocamphor; about 80% of the starting material (3,3-dibromocamphor) was recovered unchanged and about 17% of pyridinium hydrobromide was isolated and identified by its P.M.R. spectrum.

3. s-COLLIDINE

3,3-Dibromocamphor and s-collidine in 1:5 mole ratio at 135° for 117 hours in a sealed tube gave a black tarry mass. This was subjected to trituration and Soxhlet extraction with thoroughly dried solvents, diethyl ether and chloroform. The diethyl ether soluble fraction was washed with dilute acid to get rid of any unreacted base and gave 89.5% of crude monobromocamphor. On chromatography over neutral alumina the forerun from petroleum ether gave pure 3-monobromocamphor (80% based on starting material). Subsequent elution with ether gave a small quantity (~10% of the material subjected to chromatography) of a brown oily liquid which was not identified. The diethyl ether insoluble, chloroform soluble brown crystalline material, isolated in 20 mole percent excess calculated on dibromocamphor, was shown to be s-collidinium hydrobromide by P.M.R. and infrared spectroscopy, comparison with an authentic sample and by elemental analysis. An intractable black crystalline mass remained in the Soxhlet residues and was found to be insoluble in common organic solvents and in concentrated sulfuric

acid and amounted to less than 5% of the total solid products by weight. Elemental analysis showed this material to contain C, H, N and Br. A careful analysis of all the bromine containing products was done and the percentage yields calculated on the basis of the total bromine present in the starting material.

Products	% (as bromine)	% Theoretical required
3-Monobromocamphor	40.01	50
s-Collidiniumhydrobromide	53.81	50
Intractable solid	3.36	--
Polar material	Nil	--
Total	97.18	100
Unaccounted	2.82	0

In a competitive experiment the relative rates of decomposition of the two epimeric 3-bromo-3-chlorocamphors were found to be identical (no change in the proportions of recovered epimers).

4. DISCUSSION

Reductive dehalogenations of α-haloketones by tertiary amines are important reactions since they accompany preparative procedures such as dehydrohalogenations. Their mode of reaction has some unsettled points such as the source of proton when the reactions are carried out in neat solutions of the amine with exclusion of moisture. In the use of pyridine derivatives there has been some controversy in the past. Recently Warnhoff and Marshall[108] from these laboratories have conclusively demonstrated some reductive dehalogenation of 2-α-bromocholestane-3-one by substituted pyridines.

In the present studies we found that reductive dehalogenation of 3,3-dihalocamphors is the major reaction with N-methylpiperidine and s-collidine. The reaction with pyridine was very slow.

In the reaction of N-methylpiperidine with dihalocamphors it appears that the base itself provides the proton required for reductive dehalogenation, presumably forming N-methylenepiperidinium bromide. This could be isolated in the initial stages of the reaction at room temperature. The reductive dehalogenation however does not show any selectivity for exo and endo orientations of bromine.

With s-collidine as the dehalogenating agent careful analysis revealed that more bromine is present in the products as s-collidinium hydrobromide than could be accounted for by the removal of one atom of bromine for each molecule of 3,3-dibromocamphor. It is suggested that part of the dihaloketone (perhaps less than 20%) is decomposed and provides both atoms of bromine to form the excess s-collidinium hydrobromide. This presumably also provides the protons required in the reductive debromination, as well as for the formation of s-collidinium hydrobromide. The reaction of pyridine probably also follows a similar path. No selectivity was observed in the reductive dehalogenation of 3-bromo-3-chlorocamphors by s-collidine.

F. DEHALOGENATION BY TRI-n-BUTYLTINHYDRIDE

1. PRODUCTS AND RATES

Treatment of 3,3-dibromocamphor with one equivalent of tributyltinhydride at 25° in ether under nitrogen resulted in essen-

tially complete removal of one atom of bromine per mole. The 3-monobromocamphor contained 28% of exo epimer and 72% of endo epimer. Under the same conditions the two epimeric 3-bromo-3-chlorocamphors showed only debromination and no sign of dechlorination at all. The proportions of the epimeric 3-monochlorocamphors formed from both the 3,3-dihalocamphors are identical within experimental error, 3-endo-chlorocamphor 72± 3%, 3-exo-chlorocamphor 28 ± 3%. Identical behaviour was observed in cyclohexane solvent.

Reductive dehalogenation in cyclohexane was found to be a much slower reaction than in diethyl ether. The extent of dehalogenation was followed by determining the ratio of 3-monohalocamphor formed from cut-and-weigh technique of relative intensity measurement of P.M.R. signals. The data were plotted as log (100-% reaction) against time. Reasonably linear plots were obtained for 3,3-dibromocamphor and the two epimeric 3-bromo-3-chlorocamphors. The slopes for the two 3-bromo-3-chlorocamphors, under the same conditions are identical. The dehalogenation follows overall first order kinetics, $t_{\frac{1}{2}}$ for 3,3-dibromocamphor is 690 min., and for the two chlorobromo epimers is 2600 min., i.e. relative first order rate constants are 4:1:1 respectively. An independent run using C-4 H area measurements of P.M.R. signals from aliquots drawn at intervals again gave identical slopes for the first order rate plots for the two epimeric 3-bromo-3-chlorocamphors, but the absolute magnitude of the first order rate constants k^1 were different from the earlier measurements.

2. DISCUSSION

Some interesting features of this reaction are (i) there is no stereochemical preference in the removal of bromine in the two epimeric 3-bromo-3-chlorocamphors (b) both the epimeric dihalocamphors gave the same ratio of epimeric monochlorocamphors in which the proportion of exo epimer was much larger than that present either in the reactions in which an enol is believed to be an intermediate (eg. triphenylphosphine dehalogenations give almost exclusively 3-endo monohalocamphor) or where the first formed epimers are equilibrated and (iii) the reaction follows reasonable first order kinetics.

Reductive dehalogenation by tributyltinhydride has been a subject of extensive studies though mechanistic information available is not as extensive. It is fairly well agreed that dehalogenation of alkyl halides proceeds through a radical abstraction mechanism.[109] It is not settled whether in α-haloketones the free radical attack is on halogen or on the carbonyl group. This alternative possibility of the attack on the carbonyl group has to be considered since the alkyltin hydrides can cause reduction of the carbonyl group, although they do so at higher temperatures.[109a] To account for the observed kinetics one could use the scheme offered by Kuivila, et. al.[109a-c] Writing CXY for dihalocamphors (X=Br, Y=Br or Cl). $In^{\bullet}$ for initiator radical and dots denoting radical species,

$$In^{\bullet} + HSnBu_3 \xrightarrow{k_1} In\,H + {}^{\bullet}SnBu_3 \qquad (1)$$

$$CXY + {}^{\bullet}SnBu_3 \xrightarrow{k_2} {}^{\bullet}CY + XSnBu_3 \qquad (2)$$

$${}^{\bullet}CY + HSnBu_3 \xrightarrow{k_3} CHY + {}^{\bullet}SnBu_3 \qquad (3)$$

Assuming that all the steps are irreversible,

$$\text{rate of formation of product} = k_3 \left[{}^{\bullet}CY\right]\left[HSnBu_3\right] \qquad (4)$$

Solving for the concentration of $^{\bullet}CY$, assuming a steady state in $^{\bullet}CY$, one gets a pseudo first order expression,

$$\text{rate} = k_2 \left[CXY\right]\left[{}^{\bullet}SnBu_3\right] \qquad (5)$$

Since $^{\bullet}SnBu_3$ is being regenerated at the last step, the expression can be rewritten as

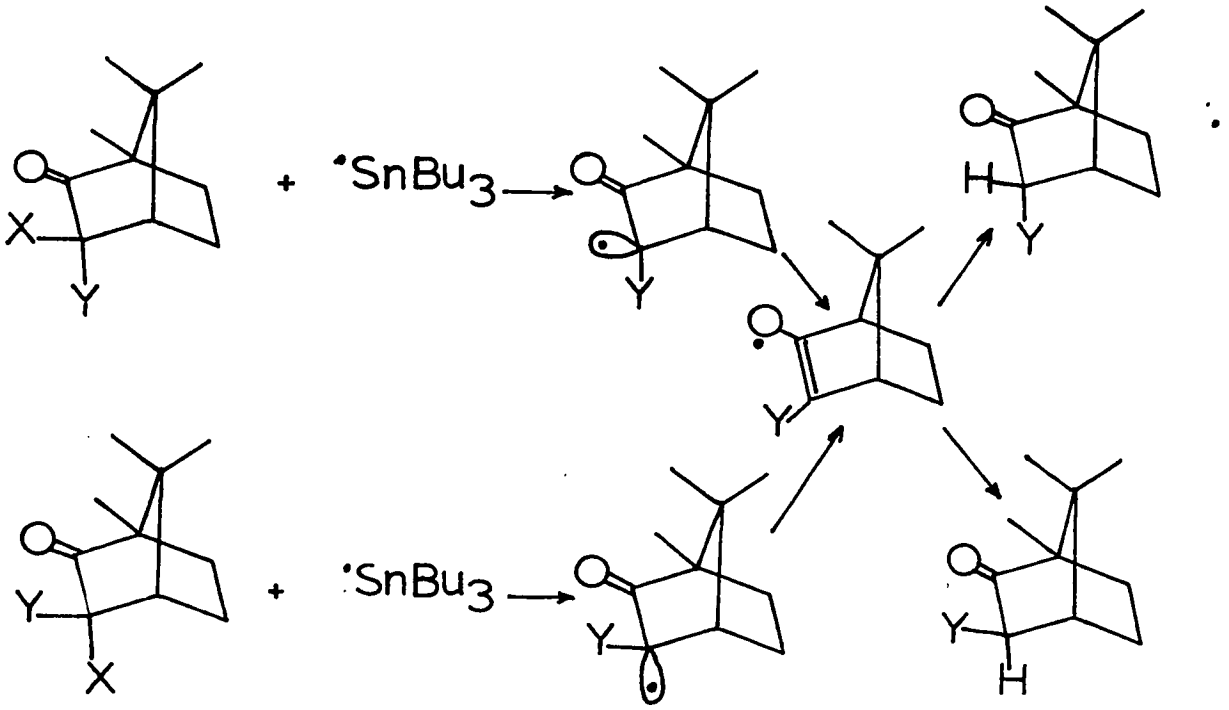
$$\text{rate} = k^1 \left[CXY\right] \qquad (6)$$

where k^1 is a pseudo first order rate constant whose dimension depends on the initial concentration of the initiator and tributyltin hydride. The kinetic data fit this expression. The fact that the reaction conditions alter the magnitude of the rate constant would be in accord, the magnitude depending on initial concentration of radical initiators. A radical abstraction mechanism would also explain exclusive debromination, since abstraction of bromine is known to be favoured over removal of chlorine in a radical path.[110]

The non selectivity in the abstraction of exo bromine compared to endo bromine is interesting and is worth some speculation regarding the nature of transition state. If we accept Paul von R. Schleyer's explanation[111] for directional selectivity in exo approach and exo departure of substituents in bornane skeleton being due to torsional effects,* this explanation must be recon-

* For further discussion of "torsional effects" see the general conclusion (Section IX).

ciled with the results in radical dehalogenation of haloketones. Radical studies on the bornane skeleton are limited. We offer the suggestion that debromination of 3-bromo-3-chlorocamphor in the transition state does not involve simultaneous movement of the remaining substituent on C-3. This statement implies that the bornane radical transition state is sp^3 like. If this is true it would automatically mean that torsional effects would not control the rate of bromine removal. The only limitation would be steric accessibility of bromine by the reagent. Judging from the rate of debromination of the two epimers there is no steric limitation either. The next question concerns the identical ratios of the monochloro epimers that are formed from the two epimeric 3-bromo-3-chlorocamphors. This result together with Schleyers[111] postulate suggests that the first formed radical is non planar and must have the same orientation as of bromine in the substrate. This apparently is long lived enough to get equilibrated (either by a planar radical, or else by an inverting non planar one) to account for the identical product distribution from both the radicals. Such equilibration can readily occur because of conjugation with carbonyl group. However, there is some evidence that an <u>enol</u> (from attachment of a hydrogen atom to oxygen in the initially formed radical) could not be an intermediate, since enols, in neutral media, give almost exclusively the <u>endo</u> epimer of 3-monohalocamphor. On the basis of the above argument the following scheme is presented:



Equilibrating radicals have been demonstrated[112] in the dehalogenation of 9-halodecalins by tributyltinhydride. The kinetic evidence is also consistent with the known behaviour of the reagent.[113]

VII

ENOLATES AND ENOL DERIVATIVES OF 3-HALOCAMPHORS AND CAMPHOR

A. REACTION OF ALKYLLITHIUMS WITH 3-HALOCAMPHORS

1. INTRODUCTION

Enolates of 3-halocamphors could be generated either by the action of sodium hydride or of alkyllithiums on 3-halocamphors. The reaction with sodium hydride was sluggish presumably due to low solubility of the reagent in the solvents used. Alkyllithiums on the other hand are fairly soluble in hydrocarbons as well as ether solvents and are also readily available. The action of alkyllithiums on 3-halocamphors was explored extensively.

An alkylmetal can react with a 3-halocamphor in several ways. Removal of C-3 hydrogen would give the desired enolate of 3-halocamphor. Halogen-metal exchange[114] between the alkylmetal and 3-halocamphor would form the enolate of camphor and alkyl halide. An attack on the carbonyl carbon would result in a 2-alkylbornanol. Several other side reactions can occur. For example the alkyl halide formed in the halogen-metal exchange can alkylate the enolate of camphor, the overall reaction being similar to that from a Wurtz type coupling. Lipp, et al.[115] studied the action of phenyllithium on 3-halocamphors and reported considerable dehalogenation (metal-halogen exchange), apart from phenyl addition to the haloketone. Bernstein[116] examined the action of phenyllithium on 3-iodocamphor. The reaction was followed by estimating the total

alkali titre against time. A progressive decrease in alkali titre was observed and was explained by assuming a "coupling" (Wurtz type?) between the halocamphor and phenyllithium. We anticipated that some amount of selectivity towards the desired enolisation reaction might be attained by altering solvents, concentrations, temperature and the nature of the alkyl group if necessary.

2. RESULTS AND DISCUSSION

Exploratory experiments were carried out to determine the effect of variables on competing reactions of alkyllithiums with 3-halocamphors. The reactions were carried out under nitrogen and after quenching with water the neutral products were extracted with petroleum ether and examined by P.M.R. spectroscopy and thin layer chromatography. The aqueous extracts were examined for halide ions. The enolate was also trapped either by halogenating agents or acylating agents. The results appear in Table XII. Considerable dehalogenation occurred in hydrocarbon solvents (entries 1-3) and in diethyl ether (entry 4). At room temperature or above debromination was a minor reaction in tetrahydrofuran, the major reaction ($\sim 65\%$) being enolisation of 3-bromocamphor (entries 5-9). At -70° in tetrahydrofuran dehalogenation again became the major reaction (entries 10, 11). We did not find evidence for any "coupling"[116] between bromocamphor and alkyllithium. In contrast to the behaviour of 3-bromocamphor (and the reported behaviour of 3-iodocamphor), reaction of 3-chlorocamphor in tetrahydrofuran solution with butyllithium led to exclusive formation of 3-chlorocamphor enolate which was trapped as its enol

TABLE XII

NO.	SUBSTRATE/ CONCENTRATION	SOLVENT AND CONDITIONS	BASE/ CONCENTRATION	DEHALOGENATION %	3-H REMOVAL %	HALIDE IONS %
1	3-endo-Bromocamphor 0.1M	n-Hexane 2 hrs. R.T.	n-BuLi 0.096M	60	40	12.6
2	"	"	" 0.192M	Not estimated		40
3	"	" 12 hrs. R.T.	" 0.29M	"	"	57.9
4	"	Et_2O 2 hrs. 10°	" 0.2M	80	20	-
5	"	THF 4 hrs. R.T.	" 0.096M	31.5	68.5	9.8
6	"	"	" 0.192M	33.5	66.5	33.2
7	"	"	" 0.29M	Not estimated		33.5
8	"	" 8 hrs. R.T.	" 0.2M	"	"	32.6
9	"	" 9 hrs. R.T.	" 0.3M	37.8	62.2	-
10	"	" 4 hrs. -70°	" 0.192M	80	20	72
*11	"	" 2 hrs. -70°	"	86.2	13.8	-
**12	3-endo-chloro camphor 0.2M	THF 20 min. R.T.	n-BuLi 0.25M	Nil	84%	-

* Quenched with sulfuryl chloride after cooling. Figures of enolisation are based on percent monochlorocamphor isolated (composition of monochlorocamphor: 77% exo-chloro, 23% endo-chloro).

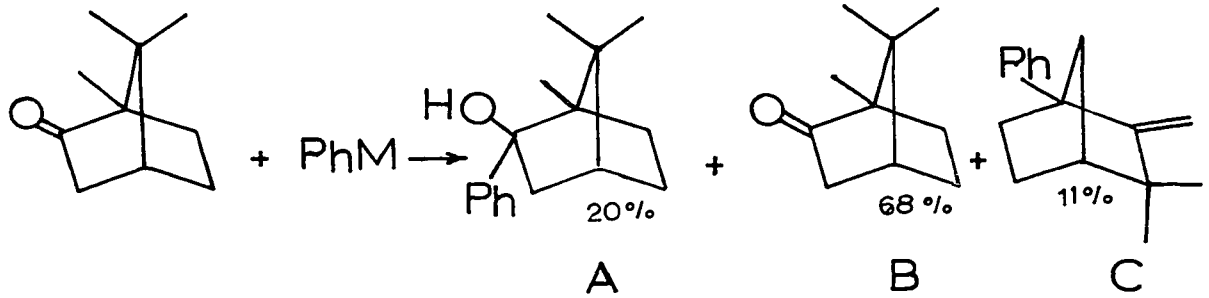
** Cooled to -50° and quenched with acetic anhydride. Figure of enolisation is based on actual quantity of 3-chlorocamphor enol acetate isolated. No camphor enol acetate was detected.

ester. No dechlorination was detected.

B. REACTION OF ALKYLLITHIUMS WITH CAMPHOR AND RELATED KETONES

1. INTRODUCTION

From a preparative viewpoint reactions of camphor with alkylmetals are interesting. Mälkönen[72,117,118] has studied the reaction of Grignard reagents with camphor in several solvents. The Grignard reagents can either attack the C-3 hydrogen thereby forming the enolate of camphor or else attack the carbonyl carbon to give a tertiary alcohol. If the alkyl group of the Grignard reagent has a β-hydrogen the attack on carbonyl carbon quite often results in the reduction of camphor to bornanols. The carbonyl addition or the reduction of the carbonyl group is reported to range between 0-90% depending on the Grignard reagent, solvent and concentrations. The major competing reaction is enolisation of camphor. Vinyl Grignard[119,120] reagent gives carbonyl addition to the extent of 48% in tetrahydrofuran solution. Bernstein[121] examined the action of phenylmagnesium bromide and phenyllithium on camphor and identified three products from this reaction:



M = MgBr or Li.

The 68% of starting material recovered was assumed to have arisen from the enolate of camphor on aqueous work up. The phenyl addition products (A and C) totalled 31%. We studied the action of

butyllithium on camphor, norcamphor and 2,5-dioxobornane under the conditions in which 3-halocamphors had given optimum yields of enolates.

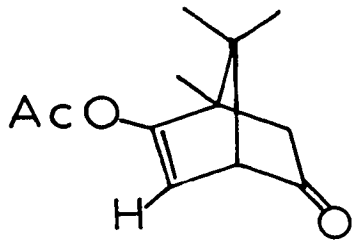
2. RESULTS AND DISCUSSION

The reaction of camphor with n-butyllithium was carried out at room temperature in tetrahydrofuran. The products were identified after quenching with suitable reagents to trap the enolate. The reaction mixture was cooled to -50° and the acylating agents (acetic anhydride and ethyl chloroformate) were introduced. Acetylation gave 80% (minimum figure) of camphor enol acetate. Reaction with ethyl chloroformate gave 72% of camphor enol ethyl carbonate. The reaction with methyliodide was much slower and yielded ~ 78% of 3-endo-methylcamphor. When the reaction mixture of camphor and butyllithium was poured over solid carbon dioxide, an epimeric mixture of camphor-3-carboxylic acid was obtained in well over 70% yield.* Thus it is evident that in these reactions the enolates of camphor must have formed to the extent of at least 70%.

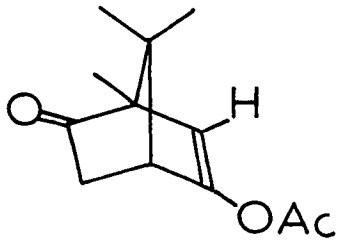
When norbornanone was reacted with butyllithium at room temperature in tetrahydrofuran, the reaction mixture cooled to -50° and acetic anhydride was added to the reaction mixture, work up gave three products. The major product from this reaction was 2-n-butyl-2-acetoxynorbornane obtained in ~ 80% yield. A minor product (~ 2%) was 2-acetyl-norbornane. The third product was not identified. Under identical conditions 2,5-dioxobornane gave a crude liquid product after work up. The P.M.R. spectrum of the crude had two doublets in the vinylic region, centred at 5.59

* This is probably the best method for preparing camphor-3-carboxylic acid at present.

p.p.m. (J = 3.5 c.p.s.) and at 5.1 p.p.m. (J = 1.5 c.p.s.). The acetoxyl methyls appeared at 2.14 p.p.m. and 2.05 p.p.m. respectively. The other (quaternary methyl) signals appeared at 1.18, 1.03, 1.0, 0.97 and 0.87 p.p.m. (s). On the basis of the two vinylic protons and the two acetoxyl methyls the mixture was tentatively assumed to contain two products, D and E arising from O-acylation of the two possible enolates:



D



E

The vinylic proton in D ought to be a doublet similar to that in camphor enol acetate. The signal at 5.59 p.p.m. was assigned to this. The vinylic proton in E from first approximations ought to be a singlet, but a long range allylic coupling with C-4 proton can cause this to appear as a doublet with small coupling. The signal at 5.1 p.p.m. was tentatively assigned to this. The reason for an upfield shift of $\sim$ 0.5 p.p.m. is not obvious. No attempt was made to isolate the pure products or characterise them. The relative intensities of 5.59 and 5.1 p.p.m. signals were 14.5:85.5.

C. ENOL ACETATES OF CAMPHOR DERIVATIVES

1. 3-HALOCAMPHOR ENOL ACETATES

The reaction of 3-halocamphors with alkyllithiums under optimum conditions gave 3-halocamphor enolates which could be trapped with acetic anhydride and led to the preparation of 3-halocamphor enol acetates. These vinylic halide esters are at

present accessible only by this route. In tetrahydrofuran solution, room temperature reaction of 3-endo-bromocamphor with n-butyllithium followed by acylation at -50° gave 3-bromocamphor enol acetate (77.7%), camphor enol acetate (18.3%) and 3-bromocamphor (4%). 3-Bromocamphor enol acetate and camphor enol acetate were separated by fractional distillation and purified by chromatography over neutral alumina. Under identical conditions the crude neutral product isolated from the reaction of 3-chlorocamphor was almost entirely 3-chlorocamphor enol acetate with a small amount ($\sim$ 3.5%) of 3-chlorocamphor. Distillation followed by chromatographic purification yielded $>$ 80% of 3-chlorocamphor enol acetate.

3-Bromocamphor enol acetate was inert to hydrogen bromide in diethyl ether solution as well as to hydrogen chloride in carbon tetrachloride solution at room temperature for over 30 minutes. In acetic acid solution reaction with hydrogen bromide for 10 hours at room temperature gave 3-bromocamphor which was almost exclusively the endo epimer. On treatment with traces of alkali this passed into the usual mixture of epimeric 3-bromocamphors (containing over 10% of 3-exo-bromocamphor).

3-Chloro- and 3-bromocamphor enol acetates react slowly with halogens and catalysts are needed for preparative halogenations. The stereochemistry of these halogenations has been described in section IV.

3-Bromocamphor enol acetate was hydrolysed cleanly into 3-bromocamphor when refluxed with 5% methanolic potassium hydroxide for 15 minutes. On attempted reductive dehalogenation of this vinylic halide ester with aluminium amalgam in aqueous tetrahydro-

furan for 2 hours at room temperature and with tributyl tin hydride in ether for two hours at room temperature, no dehalogenation occurred. 3-Bromocamphor enol acetate was recovered unchanged.

2. CAMPHOR ENOL ACETATE

(a) Preparation

W.D. Chambers, [73,74] in these laboratories has investigated the synthesis of camphor enol acetate by more conventional procedures, such as acetic anhydride and p-toluenesulfonic acid at 138° and 200°, acetic anhydride and sulfuric acid at 160°, acetic anhydride and boron trifluoride at 138° and isopropenyl acetate and sulfuric acid at 96° and did not find any evidence of camphor enol acetate formation. While reexamining the reported[122] formation of camphor enol acetate from lead tetracetate oxidation of camphene he found that the alleged camphor enol acetate of the Japanese workers[122] was in fact camphor 2,6-homoenol acetate, which he demonstrated to arise from tricyclene, a contaminant in commercial samples of camphene. We found that camphene, free of tricyclene formed only traces of the homoenol acetate, if any at all. In the present work we also found that enol esters of camphor did not form on refluxing camphor with acetyl chloride or benzoyl chloride, contrary to the literature report.[123]

Camphor enol acetate was isolated as a side product in the acetylation of the reaction mixture of 3-bromocamphor and butyllithium. In later experiments the reaction of n-butyllithium with camphor in tetrahydrofuran solution at room temperature followed by acetylation with acetic anhydride at -50° gave in the neutral, petroleum ether soluble fraction only camphor enol acetate and

camphor. No evidence for C-acylation or attack on the carbonyl group was obtained. The proportion of recovered camphor ranged between 5-20%. This observation provided the basis for a preparative procedure for camphor enol acetate. The enol ester was purified by distillation at reduced pressures followed by rapid chromatography over neutral grade III or IV alumina, the latter treatment being necessary to get rid of camphor. The yields of camphor enol acetate in preparative experiments ranged above 80%.

(b) REACTIONS

D-Camphor enol acetate, acetic acid and sodium acetate in 1:1:2 molar ratio in excess acetic anhydride (20X) at 150° for 4 hours gave a petroleum ether soluble product which contained camphor with no trace of the enol acetate left. The work up was completely devoid of water at all stages. When D-camphor enol acetate and acetone in 1:1 mole ratio along with a catalytic amount ($\sim$ 6%) of p-toluenesulfonic acid were heated for 10 hours at 120°, the hexane soluble products after the removal of the solvent yielded only camphor quantitatively with no trace of enol acetate left.

Solutions of camphor enol acetate were prepared in P.M.R. tubes and hydrogen halide passed into it. In acetyl chloride solution the action of hydrogen chloride resulted in quantitative conversion to camphor in 5 minutes at room temperature. In carbon tetrachloride solution the action of hydrogen chloride resulted in complete disappearance of camphor enol acetate in less than 10 minutes. The only products detected were camphor and acetyl chloride.

Camphor enol acetate reacted with chlorine and bromine almost instantaneously and thus allowed the enol acetate to be

titrated with bromine solutions at room temperature. Reaction with elemental iodine on the other hand is a sluggish reaction. The stereochemistry of these halogenations is discussed in section VIII.

Camphor enol acetate reacted with mercuric acetate in methanol at room temperature in 2 hours to give 73% of 3-acetoxymercury camphor. Reaction of 3-acetoxy-mercury camphor with iodine gave 3-iodocamphor in quantitative yields.

In acetone solution at room temperature in the presence of aqueous sodium bicarbonate, D-camphor enol acetate reacted with potassium permanganate to give camphorquinone in 95% yield.

3. DISCUSSION

In its reactions with electrophilic reagents such as hydrogen halides, halogens, etc., camphor enol acetate displays a far greater degree of reactivity than either the bromocamphor enol acetate or chlorocamphor enol acetate. The diminished reactivity in the latter two derivatives of camphor enol acetate is expected due to electronegativity of the substituents (bromine and chlorine).

The equilibrium in the camphor enol acetate - acetic acid - acetic anhydride system and in the camphor enol acetate - acetone system lies entirely towards camphor. In the first system camphor enol acetate must have abstracted the acid proton from acetic acid forming camphor and acetic anhydride. In the second case a proton abstraction from acetone would have resulted in acylation of acetone, presumably forming isopropenyl acetate. Camphor enol acetate might find use as a powerful but mild acylating agent.

The usefulness of the high reactivity of camphor enol

acetate in preparing 3-substituted camphors is perhaps best illustrated in the preparation of 3-acetoxymercury camphor from which derivatives such as 3-iodocamphor could be conveniently prepared.

VIII

HALOGENATION AND ENOLISATION OF CAMPHOR

A. INTRODUCTION

The bromination and chlorination of camphor are acid catalysed reactions, involving the enol of camphor as an intermediate. Earlier work by Lowry and his collaborators,[34-36], Marsh[24], Kipping[30] and Pope[31] indicated that the crude monohalogenation product obtained on direct halogenation contained a high proportion of 3-exo-halocamphor. In alkaline solutions rapid epimerisation occurred leading to an equilibrium mixture in which the proportion of 3-endo-epimer predominated to the extent of $\sim$90% of the epimeric mixture. In view of our earlier work on the halogenation of 3-halocamphors, it became desirable to examine the halogenation of camphor itself under kinetically controlled conditions in order to elucidate the directional control in the absence of C-3 substituents. Similar information was also sought in the halogenation of camphor enolate and camphor enol acetate. It was also intended to examine the directional preference, if any, in the enolisation of camphor and in the protonation (or deuteration) of camphor enolate under kinetically controlled conditions.

B. HALOGENATION OF CAMPHOR AND ITS ENOL DERIVATIVES

1. HALOGENATION THROUGH ENOL

Bromination of camphor in a buffered system, for instance in acetic acid - sodium acetate, is a very sluggish reaction. J. D.

Roberts and W. G. Woods[37] in 1957 reported that at 35° in this system the rate of bromination of camphor was at least a factor of 33 slower than that of norcamphor. This system is not suitable for the purposes of the present investigation since the enolisation of bromocamphor, as indicated by its rate of bromination is greater than that of camphor. Corey[3g] described a technique for carrying out kinetically controlled halogenation of ketones, by trapping any enol or enolate that might form from monohaloketone. The halogenation is carried out in presence of a large excess of bromine and the epimeric ratio of monohaloketones is looked into. The enol of first formed monohaloketone, if it did form, would react with excess bromine and would not interfere with the first formed ratio of monohaloketones.*

Bromination of camphor was carried out in the presence of <u>excess</u> bromine and the crude mixture containing excess bromine was examined by P.M.R. spectroscopy to obtain the ratio of epimeric 3-bromocamphors from the intensities of the 3-methine proton signals. Treatment of D-camphor with four equivalents of bromine in chloroform at room temperature, catalysed by traces of hydrogen bromide, did not show any sign of bromination over 48 hours. No bromination was detected in refluxing carbon tetrachloride solution with camphor and bromine in a proportion of one to four moles for a period of 150 hours. In acetic acid at steam bath temperatures (95°-100°) for 1 hour no reaction was detected

* This reasoning is based on the premise that both the epimers would get <u>enolised</u> at the same rate if they did. One could argue that the two epimeric monohaloketones may not epimerise at the same rate, and the consequent bromination of the enol from the faster enolising epimer would deplete the mixture with regard to this epimer.

between camphor and bromine. With added hydrogen bromide under these conditions monobrominated camphor was detected. The proportion of 3-exo-bromocamphor was 57.8% and 3-endo-bromocamphor 42.4%.

In the same solvent system, containing excess chlorine and camphor and using hydrogen chloride as catalyst no chlorinated camphor was detected after 24 hours at room temperature.

Hydrogen bromide catalysed bromination of camphor in acetic acid must have involved the enol of camphor; the preference for exo approach of the entering halogen in this case is 1.37 over 1 for endo.

2. HALOGENATION OF CAMPHOR ENOL ACETATE

A solution of D-camphor enol acetate in acetonitrile was treated with a solution of chlorine in carbon tetrachloride giving 45% of 3-exo-chlorocamphor and 55% of 3-endo-chlorocamphor. The ratio of exo to endo entry of chlorine is 0.82. Bromination of D-camphor enol acetate under identical conditions gave 36% of 3-exo-bromocamphor and 64% of 3-endo-bromocamphor. The ratio of exo to endo entry of bromine is 0.55.

3. HALOGENATION OF THE LITHIUM ENOLATE OF CAMPHOR

The lithium enolate of camphor was generated by the action of n-butyllithium on camphor in tetrahydrofuran at room temperature. The enolate was added to a solution of halogen in petroleum ether with vigorous stirring. The procedure (see Experimental) ensures excess halogen at all times during and after the addition of enolate. Chlorination gave 75.0% of 3-exo-chlorocamphor and 25.0% of 3-endo-chlorocamphor. The ratio of exo to endo entry of chlorine is 3:1. Bromination under identical conditions gave 70% of 3-exo-bromocamphor and 30% of 3-endo-bromocamphor. The ratio of exo to

endo entry of bromine is 2.33:1.

4. DISCUSSION

Under kinetically controlled conditions the ratio of 3-exo-haloepimer and 3-endo-haloepimer represents the relative rates of halogenation from exo direction (rate constant, k exo) and endo direction (rate constant, k endo). These ratios are expressed below:

SUBSTRATE/INTERMEDIATE	BROMINATION k exo/k endo	CHLORINATION k exo/k endo
Lithium enolate of camphor	2.33	3.1
Camphor enol	1.37	---
Camphor enol acetate	0.55	0.82

The maximum exo preference for the entry of the reagent is exhibited by enolate anion and the minimum by the enol ester. Between bromine and chlorine, a larger proportion of chlorine enters from the exo side. We suggest that the stereoelectronic factor favours the exo entry of the substituent and that the steric factor opposes the exo entry. If we accept that the major steric factor has its origin in the interactions between the C-8 methyl group and the entering reagent a lesser tendency for exo entry should exist with increasing bulk of the reagent. The smaller k exo/k endo ratio for bromination compared to that of chlorination is consistent with this suggestion. Both the enol as well as lithium enolate of camphor exhibited a preference for exo entry while the enol acetate did not. We suggest that the high nucleophilicity of the enol or enolate make it possible for the carbon halogen bond to form to a greater extent at a greater distance such that the full complement of the stereoelectronic factor is observed with much less interfer-

ence from the steric influence of the C-8 methyl group. The enol acetates on the other hand behave like alkenes, requiring a much closer approach of the reagent before the transition state is reached. Such close approach of the reagent would be subject to increasing control of the steric factor.

C. DEUTERATION OF CAMPHOR ENOLATE AND ENOLISATION OF CAMPHOR

1. INTRODUCTION

Thomas and Willhalm[124] observed that base catalysed deuterium exchange of camphor gives 85% of a monodeuterated species which was shown by conversion to 2-*exo*-bornanol and examination of the 2-*endo* methine proton signal of the latter to be largely 3-*exo* deuterio camphor. Subsequently Meinwald, *et al.*[125], carried out a more detailed examination of hydrogen-deuterium exchange in camphor. The earlier observation on *exo* deuteration in base catalysed hydrogen-deuterium exchange was confirmed. These authors also treated 3,3-dideuteriocamphor with dioxane - water in the presence of hydroxide ion and have shown that 3-*endo*-deuterio camphor results in this exchange. These results have drawn the attention of several chemists[126,127] and have been instrumental in eliciting some interesting rationales.[111,127]

The exchange reactions were carried out by the earlier workers in systems containing a base and its conjugate acid which could readily donate a proton (for example hydroxide ion in water and methoxide ion in methanol-O-d_1). The conditons are therefore "equilibrating". The only information one can obtain from these studies is that the intermediate, enol or enolate, shows selectivity in protonation - deuteration from the *exo* side. No information is available *per se*, except by invoking microscopic reversi-

bility, as to whether there is any preference for the removal of the exo or endo proton in the enolisation step. In continuance of our studies on halogenation and dehalogenation of camphor it was desirable to obtain information on the related subject of protonation and enolisation of camphor.

2. DEUTERATION OF LITHIUM ENOLATE OF CAMPHOR

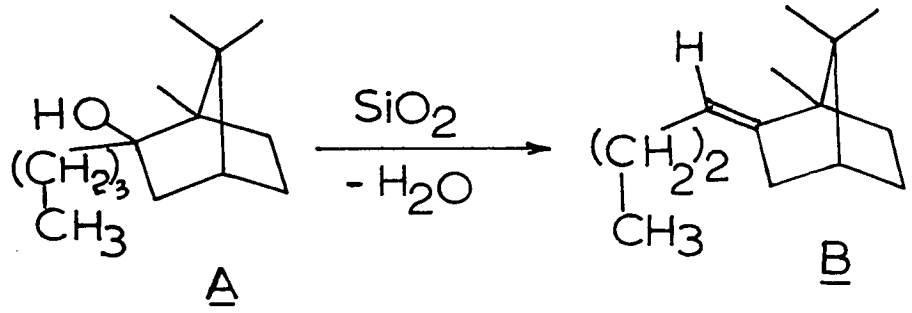
The lithium enolate of camphor was generated by the action of n-butyllithium on camphor in tetrahydrofuran and was added to a stirring solution of acetic acid-d_4-deuterium oxide. The amount of acetic acid was adjusted to keep the mixture weakly acidic throughout the addition of enolate to ensure kinetically controlled conditions. After a neutral work up camphor was isolated and the extent of deuteration was estimated by P.M.R. and mass spectrometry. The product contained 96% of camphor-d_1, 4% of camphor-d_o and no camphor-d_2.

The stereochemistry of deuteration was proved in two ways, viz. (i) a signal at 2.5 p.p.m. in the protio analogue, arising from the 3-exo proton was absent (see Plate 1) (ii) the P.M.R. spectrum of the 2-exo-bornanol obtained from reduction with lithium aluminium hydride had a doublet centred at 3.57 p.p.m., J = 8 c.p.s. instead of a doublet of doublets observed in the protio analogue. An estimate of the proportions of the epimeric camphor-3-d_1 was made from the comparison of 2-endo-methine proton signals in the spectra of 2-exo-bornanol-3-d_1 and its protio analogue. The lower limit was set at 80% of 3-exo-deuterio-2-exo-bornanol. (This value was actually greater than 80% from 100 Mc P.M.R. spectra). Hence the camphor-3-d_1 is at least 80% exo-deuterio. (See Plate 8).

3. PROTONATION OF THE LITHIUM ENOLATE OF CAMPHOR-3,3-d_2

D-Camphor-3,3-d_2 was prepared from the reductive debromination of 3,3-dibromo-D-camphor with zinc in the presence of acetic acid-d_4. The deuterium content of this material was $\sim$2 atoms per mole by P.M.R. spectroscopy. Deuterium analysis by mass spectrometry gave 83.5% camphor-d_2, 16.5 % camphor-d_1 and 0.0% camphor-d_o. Reduction with lithium aluminium hydride gave a 2-exo-bornanol whose P.M.R. spectrum showed a singlet at 3.53 p.p.m. (Plate 8). The enolate of camphor-3,3-d_2 was generated as before and protonation was carried out by reverse addition to a mixture of acetic acid and water under kinetically controlled conditions.* The deuterium content of the camphor isolated by this procedure was $\sim$0.9 atoms deuterium per mole by P.M.R. spectroscopy. Mass spectrometry gave 93% camphor-d_1 , 7% camphor-d_o and none of camphor-d_2. The stereochemistry of protonation of the 3-deuterio

* Quenching of the enolate gave an oily product containing camphor and an alcohol. Silica gel chromatography led to isolation of an unsaturated hydrocarbon (not pure), which on the basis of its P.M.R. signals was assigned the structure B. This could form from A by dehydration on the silica gel column.



A B

This reaction probably reflects the effect of deuterium primary kinetic isotope effect in changing the course of the reaction, i.e. abstraction of deuterium is enough slower than abstraction of a proton that carbonyl addition can now compete successfully.

camphor enolate was decided from the orientation of deuterium at C-3 by (a) the P.M.R. spectrum of the camphor-3-d_1 and (b) the P.M.R. spectrum of the 2-exo-bornanol obtained by reduction. The C-2 endo methine proton of the latter (Plate 8) appeared as a broad singlet (width at half height~5 c.p.s.) More direct evidence was obtained from the shape of the signal of the C-2 exo methine proton of 2-endo-bornanol which forms to the extent of 10% in lithium aluminium hydride reductions of camphor. The signal appears at 4.0 p.p.m. as a doublet of doublets (instead of ddd in 2-endo bornanol), primary coupling ~ 7 c.p.s. and a long range coupling with 6-exo proton ~1.5 c.p.s. The epimeric purity of this material was determined from the 100 Mc spectrum of the camphor-3-d_1 in which the signal arising from 3-exo-proton is well separated from the rest of the signals. The material was judged to be at least 80% of camphor-3-endo-d_1.

4. ENOLISATION OF CAMPHOR

To decide the preference, if any, in the removal of C-3 protons of camphor a different procedure had to be designed. 3-Monodeuteriocamphors with the deuterium label in a known orientation were reacted with excess butyllithium in tetrahydrofuran. As long as the alkyllithium is in excess the enolate will be present in an irreversible condition. The enolate is trapped[128] by quenching with acetic anhydride. The ratio of 3-protio- and 3-deuteriocamphor enol acetates, which is conveniently determined by scanning the 5.54 p.p.m. region in the P.M.R. spectrum and determining its intensity in relation to the acetyl methyl signal at 2.11 p.p.m., allows determination of the rate of removal of the 3-exo-proton

versus the 3-endo proton during enolisation. This method of determining rates of proton (deuteron) removal is independent of the amount of enol ester formed.

3-exo-Deuterio-D-camphor (containing ~0.95 atoms of deuterium per mole, epimeric purity ~ 80%) was treated with n-butyllithium in the reverse manner to generate the enolate.* The enolate was trapped by acetic anhydride.# The ratio of the two enol acetates by integration of the 2.11 p.p.m. and 5.54 p.p.m. signals was 46.8% of camphorenol acetate-3-d_1 and 53.2% of camphor enol acetate-d_0. In an identical manner 3-endo-deuterio-D-camphor, prepared by protonation of the enolate of D-camphor-3,3-d_2, gave 16± 1% of camphor enol acetate-d_1 and 84 ± 1% of camphor enol acetate-d_0.

5. INTERPRETATION OF RESULTS+

Let the rates of removal of 3-exo hydrogen (deuterium) be denoted by kHx (kDx) and the rates of removal of 3-endo-hydrogen (deuterium) by kHn (kDn) respectively. Assume that the labelled camphors are 100% epimerically pure.

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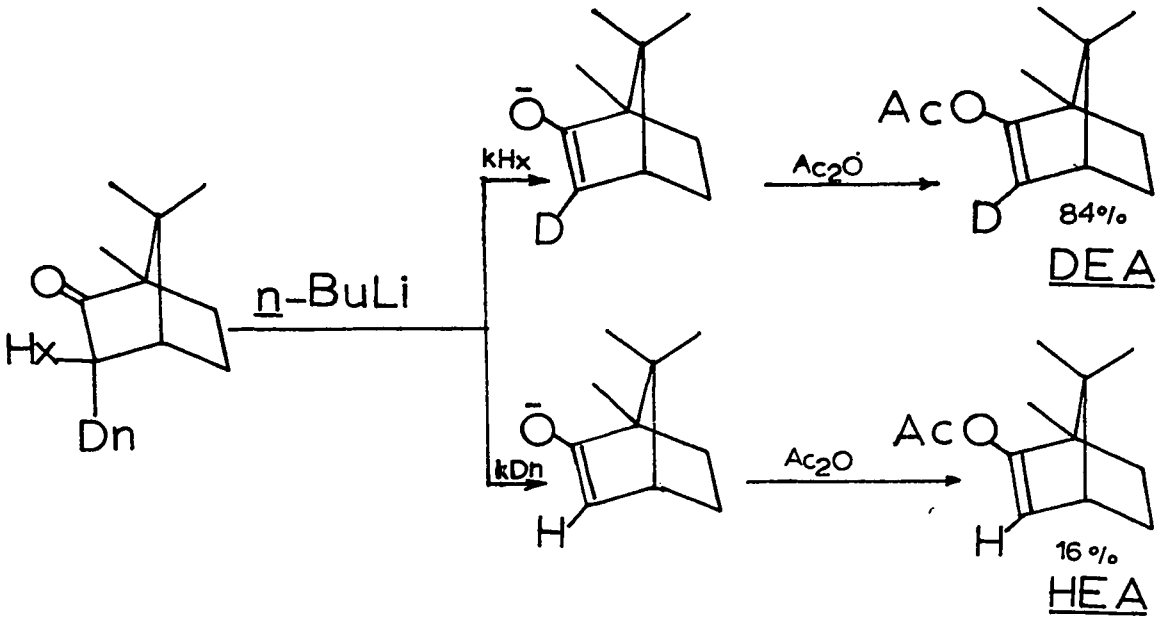
* Direct addition of base with subsequent acylation gave a different proportion of protio and deuterio enol esters. We visualise this as a rapid exchange between the first formed enolate and unreacted ketone during the addition of base. This factor is corrected, or at least minimised when the base is in excess throughout; i.e. reverse addition.

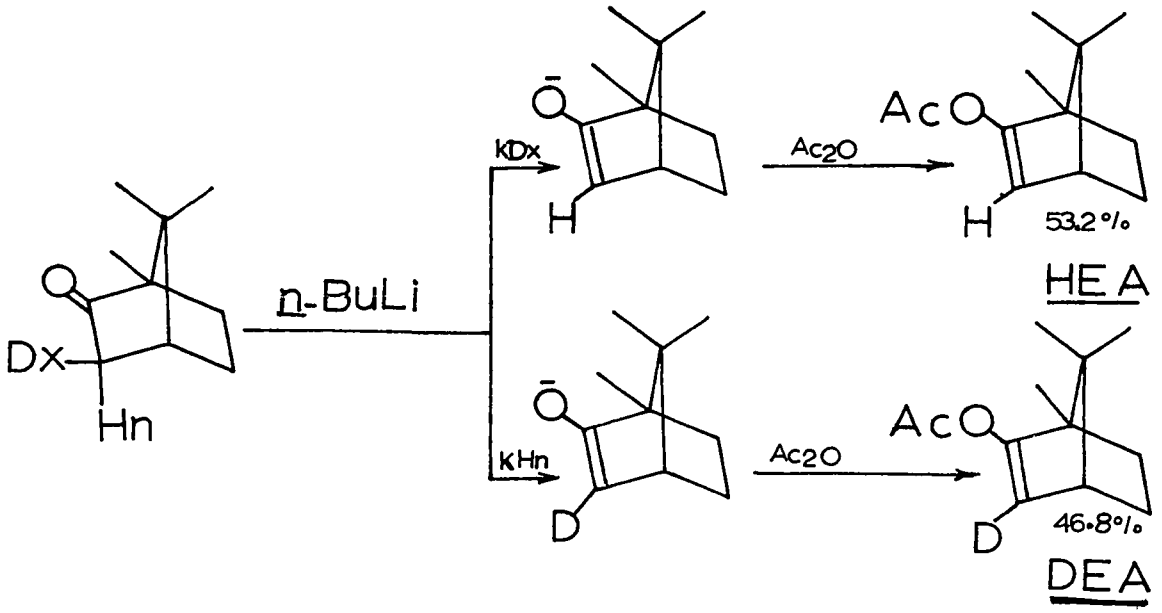
\# Apart from camphor enol acetate another material was present which on silica gel chromatography gave the same hydrocarbon as in the case of camphor-3,3-d_2. Here too attack on the carbonyl group must have occurred.

\+ Calculations are developed from a method originally described by Curtin and Kellom[129] and used by Corey.[3g]

Enolisation-enol acetylation of the two epimers is represented as under:



$$kHx/kDn = \frac{DEA}{HEA} = 84/16 \quad . \quad . \quad . \quad (1)$$



$$kDx/kHn = \frac{HEA}{DEA} = 53.2/46.8 \quad . \quad . \quad . \quad (2)$$

Multiplying (1) by (2) gives

$$\frac{kHx}{kHn} \times \frac{kDx}{kDn} = 5.96 \quad . \quad . \quad . \quad (3)$$

Assume further that the relative rates in the removal of exo versus endo hydrogen atoms are the same as in the removal of exo versus endo deuterium atoms.

i.e. $kHx/kHn = kDx/kDn$

Expression (3) can thus be rewritten as

$$\left(\frac{kHx}{kHn}\right)^2 = 5.96, \therefore \left(\frac{kHx}{kHn}\right) = \sqrt{5.96} = 2.45 \quad . \quad . \quad (4)$$

On dividing equation (1) by (2) one gets

$$\frac{kHx}{kDx} \times \frac{kHn}{kDn} = 4.61 \quad . \quad . \quad . \quad (5)$$

This equation can be solved by assuming that the magnitude of the deuterium primary kinetic isotope effect, i.e. kH/kD is the same when H and D are both exo, and when H and D are both endo, i.e.

$$\frac{kHx}{kDx} \equiv \frac{kHn}{kDn}$$

Equation (5) can then be rewritten as

$$\left(\frac{kHx}{kDx}\right)^2 = 4.61; \therefore \left(\frac{kHx}{kDx}\right) = \sqrt{4.61} = 2.15 \quad . \quad . \quad (6)$$

Apart from the assumptions already made there are two sources of error in the above method. First, the epimeric purity of the 3-monodeuteriocamphors is not known. This introduces an uncertainty in the calculated rate ratios for hydrogen/deuterium removal. Second, the effect of α-isotopic substituent (the α-secondary isotope effect) is ignored. However, this is likely to be of small magnitude, and would probably be identical for exo as well as endo positions, and hence will cancel out in calculations.

Two important conclusions from the above empirical calcula-

tions emerge:

(i) There is a selectivity of the order of 2.45 in favour of the removal of the 3-exo proton over the 3-endo proton in the formation of enolate by the action of n-butyllithium. This amounts to 71% of the 3-exo hydrogen removed against 29% of the 3-endo hydrogen removed under the conditions described. This is the first clear demonstration of the fact that the 3-exo proton is removed preferentially in the enolisation of camphor. The earlier evidence was indirect, and rested on the principle of microscopic reversibility.

(ii) The deuterium primary kinetic isotope effect is of smaller magnitude than is usually observed in the enolisation of ketones. In the hydroxyl anion catalysed exchange in acetone for example kH/kD = 9.8 at 25.2°.[130] In general, kH/kD for the base catalysed enolisation of ketones increases with increasing base strength. Deuteroxide catalysed exchange of acetone gives kH/kD = 11.2 at 25°. The theory of deuterium primary kinetic isotope effects predicts[131] that the magnitude of the effect will depend on the extent of C-H (or C-D) bond stretching in the transition state for the cleavage of C-H (D) bond. The effect is expected to be maximum when the proton or deuteron is transferred halfway between carbon and base. Since ketones have pK_A in the range of 20 units, there will be gradual increase in the isotope effect as the base strength (i.e. pK_A of the conjugate acid) approaches this value. It would be expected to decrease as base strength increases beyond this value (pK_A of conjugate acid exceeds 20 units). In liquid ammonia-sodium amide (pK_A of ammonia = 30 units) kH/kD for the ionisation of acetophenone (pK_A = 19) is reported[132]

to be 1.8-2.4 at 15 - 25°C.

In the enolisation of camphor by butyllithium we are dealing with a still stronger base, pK_A of its conjugate acid, i.e. n-butane is ~ 50 units. In the transition state one would expect almost complete transfer of proton (or deuteron) to the base. An experimental figure of $kH/kD \sim 2.15$ at room temperature ($\sim 25°$) is therefore not surprising.

IX

STEREOELECTRONIC CONTROL IN THE HALOGENATION AND RELATED REACTIONS OF CAMPHOR

A. GENERAL

In recent years considerable interest has been aroused in elucidating the mechanism of halogenation of ketones. The established view of the intermediacy of an enol or enolate in acid or base catalysed reactions might possibly turn out to be an oversimplification. Ronteix and Marquet[133] for instance have examined halogenation of optically active 2-p-carboxybenzylindanone-1. Intermediacy of the enol or enolate predicts that the asymmetric centre will be destroyed in halogenation, the consequent α-haloketone would thereby be racemic. These authors were able to demonstrate optical activity in the resulting α-haloketone. Moreover, they also noted that the extent of asymmetric halogenation is dependent on the nature of the solvent, concentration of the reactants and the nature of the halogenating agent. They have advanced arguments against asymmetric induction and propose that even though the major reaction might be occurring through the pathway of an enol or enolate as intermediate, a direct electrophilic substitution might also be occurring to account for the optical activity in the products. Christopher Rappe[134] on the other hand

has been active in investigating directional control in non-symmetrical ketones. Comparison of products in deuteration and in halogenation of these ketones in acid and base catalysed media has led him to the conclusion that different mechanisms probably operate in deuteration and in halogenation. In the base catalysed halogenation of butanone-2, between pH 5.5-7, 3-halogenated products predominated. For media with pH 12 or above, exclusively 1-haloketones resulted. Position of deuteration, however, seems to be independent of the pH of the medium. Results such as these necessitate considerations of mechanisms other than those forwarded by Lapworth[1] and subsequently elucidated by other workers (cf. section I). They do not necessarily invalidate the intermediacy of an enol or enolate in halogenation and hydrogen-deuterium exchange reactions of ketones, but do suggest caution in generalisations of mechanisms established in one case (such as rate studies on halogenations) to other cases where rigorous proof for mechanism has not been advanced.

The postulate of stereoelectronic control in acid or base catalysed halogenations and enolisation of ketones as well as deuteration (protonation) of enol or enolate is based on the premise that these reactions involve enols or enolates as intermediates. Rationalisation of first formed (kinetically controlled) products on the basis of the postulate of stereoelectronic control alone in those cases where exclusive intermediacy of an enol or an enolate has not been demonstrated is one such pitfall.

In our present studies on halogenation of camphor and its 3-halogen derivatives, dehalogenation reactions of 3,3-dihalocamphors, as well as in protonation - deuteration experiments, we

have attempted to advance arguments with regard to the type of intermediate involved. Specifically we have been concerned with the stereochemistry of the kinetically controlled products. The general approach in the present studies was to examine the reaction conditions, the stereochemistry of the substrate and stereochemistry of the products in relation to the steric disposition of the incoming electrophile. The reverse of these reactions, viz. preference for the departing substituent (dehalogenation and enolisation reactions), were also studied. As a working hypothesis, directional control inherent in the bornane skeleton, which is also exhibited in electrophilic addition reactions of bornenes, norbornenes and related compounds was called the "stereoelectronic factor." A preference for exo approach of the electrophile or a preference for the exo removal of the C-3 substituent was associated with this factor. A second type of directional control was realised and demonstrated. This manifests itself in endo approach of the electrophile. This factor has been termed "steric" and its origins were visualised in repulsive steric interactions between the C-8 methyl group, the incoming electrophile and the substituent at C-3 (relative to lesser steric interactions between C-5 and C-6 endo hydrogens, C-3 substituent and the incoming electrophile). It is the purpose of the present discussion to critically examine these two types of postulated directional controls and provide a uniform and reasonable explanation for the results in sections IV-VIII.

Stereoelectronic factors in the reaction of ketones involving enols or enolate intermediates have been defined as those direct-

ional requirements which are favoured on the grounds of maximum p-orbital overlap. In cyclohexanone these requirements are non-existent if the transition state is planar (or enol-enolate like). Only if the transition state is ketone like in the chair form of cyclohexanone, is a clear preference for axial approach (removal) versus equatorial approach (removal) of the substituent predicted. Transition states, however, can range between these two extremes. In the case of camphor the ground state of the ketone is "bisectional" with regard to the σ- plane of the carbonyl group and the substituents at C-3. The degree of p-orbital overlap in a camphor-like transition state would therefore be expected to be identical for either exo approach (departure) of the substituent or endo approach (departure). The planar transition state again does not have any directional preference on the grounds of p-orbital overlap. Yet in general the bornane skeleton, camphor itself as well as enolates of 3-substituted camphors, exhibits a clear preference for exo approach of the electrophilic substituent as well as its departure in going to enol or enolate intermediate. The term "stereoelectronic factor" is a misnomer for this factor. The most satisfactory explanation available at present for this directional tendency inherent in the bornane skeleton is due to Paul von Ragué Schleyer.[111] This factor has been named "torsional" by him and needs some elaboration here. An enol or enolate derivative of camphor has its C-3 substituent disposed at an angle of $\sim 20^{\circ}$ (towards the endo side) of C-4 hydrogen (i.e. is syn periplanar) when viewed down the C-4-C-3 axis as in figure 10a. The camphor molecule itself in the same projection has the two C-3 substituents at $\sim 60^{\circ}$.(syn clinal) with regard to the C-4 hydrogen (fig-

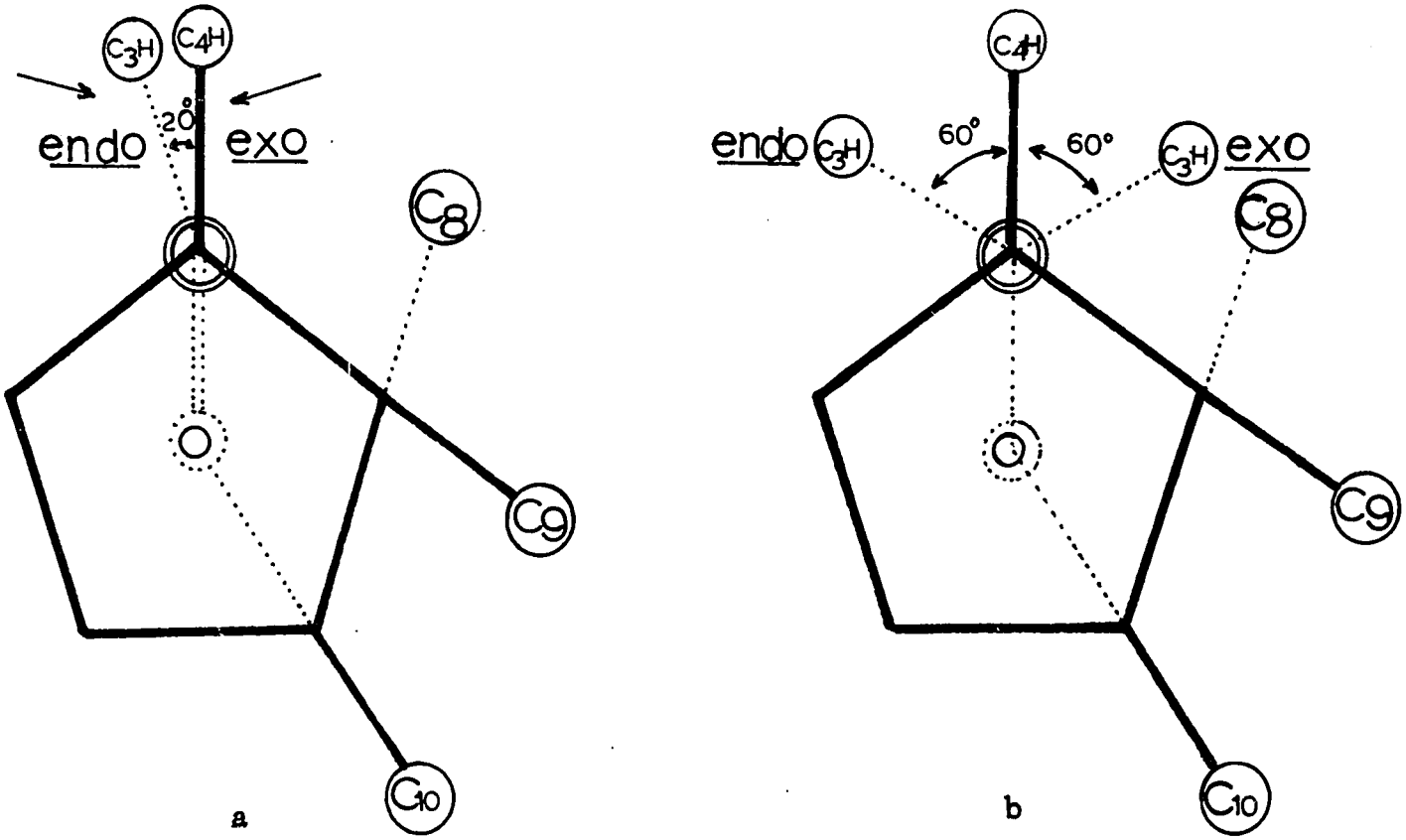


Fig. 10

Projections of camphor enol (10a) and camphor (10b) as seen down the C-4, C-3 axis.

ure 11b).

Addition to enol or enolate from the endo side results in a movement of the C-3 substituent across and past the C-4 hydrogen (eclipsing of C-3 substituent and C-4 hydrogen in the formation of products). Addition of electrophile from exo side forces the C-3 substituent away from the C-4 hydrogen (less crowding, no eclipsing). Energetically therefore exo addition is favoured. In the removal of C-3 substituents, removal of 3-exo substituent causes the movement of the erstwhile endo substituent towards C-4 hydrogen (product more crowded), removal of C-3 endo substituent causes movement of the erstwhile exo substituent past the C-4 hydrogen (ecliping) in going to the enol or enolate. Thus exo addition to a planar intermediate as well as removal of an exo substituent in going to the planar intermediate will be an energetically favoured path compared to endo addition or removal of endo substituent on grounds of the torsional factor.

The second category of directional influences, having its origin in the steric interactions between the C-8 methyl group, the C-3 substituent and the entering electrophile is more easily visualised. These repulsive interactions are much less severe when the C-3 substituent is hydrogen (or deuterium) and the entering electrophile is also small, such as proton (or deuteron). The results of our present investigation will now be examined in this light.

B. SUBSTITUTION OF CAMPHOR, ITS ENOLATE AND ENOLESTERS

Acid catalysed bromination of camphor gave 3-exo-bromocamphor preferentially. Camphor lithium enolate both in chlorination and bromination showed a preference for exo entry of the electrophile

(chlorine or bromine). A much larger preference for exo entry was found in the protonation of 3-deuteriocamphor enolate as well as in the deuteration of camphor enolate. In all these cases torsional factor prevails over the steric factor. The microscopic reverse of this reaction, viz. base catalysed enolisation, was also demonstrated to favour removal of exo proton.

Halogenation of enol acetates of camphor seem to be under increased control of steric influences (exo entry of electrophile less than 50%). Part of the reason for these results may lie in the much lower nucleophilicity of the enol acetate compared to enol or enolate. This statement implies that the halogenating agent must approach the π-cloud of the enol acetate more closely at the transition state so that the steric effect of the C-8 methyl group begins to exert its influence.

C. SUBSTITUTION OF 3-HALOCAMPHORS, THEIR ENOLATES AND ENOL ESTERS

Acid catalysed halogenation of 3-halocamphors led to preferential endo entry of the electrophile, a result which reflects the influence of steric factors in the transition state for halogenation.

Enolates of 3-halocamphors gave preferential exo entry of the entering electrophile with the use of elemental halogens and positive halogen compounds. High nucleophilicity of enolate of these camphor derivatives (implying that the transition state occurs at greater distance of C-3 and entering halogen) was invoked in minimising the influence of steric factors in halogenation. An overall control of torsional factors would then account for the observed preference for exo entry. The role of counter

ion (cation) of the enolate cannot be ignored in explaining these results. An exception was found with the use of sulfuryl chloride and 2,6-lutidine complexes of halogens. The steric bulk of these reagents would seem to explain the results.

Enol esters as postulated earlier require a close approach of the electrophile. With bulky electrophiles such as chlorine or bromine the repulsive steric interactions between C-8 methyl group, the C-3 halogen and the entering halogen are far more significant than the energetic gain through torsional influences. The results justify this view, the entering electrophile is forced to approach from the endo side almost exclusively. A proton however is not much influenced by these steric factors, the torsional factor gains influence and exo entry of the proton results in exclusive formation of 3-endo-bromocamphor on protonation of 3-bromocamphor enol acetate by hydrogen bromide in acetic acid medium.

D. DEHALOGENATION OF 3,3-DIHALOCAMPHORS

In theory reductive dehalogenation of halocamphors under the control of torsional effects should exhibit preferential removal of exo halogen provided the steric effects do not interfere with the departure of the substituent. The situation might be complicated if the approach of the dehalogenating reagent is also subject to steric interactions by C-8 methyl group.

Reductive dehalogenations were examined under the conditions where only debromination occurred. The reagents fell into 3 categories. The first category revealed a preference for the removal of exo bromine compared to endo bromine. These reagents were triphenyl phosphine and sodium borohydride. In these cases the tor-

sional influence prevails in the transition state for removal of bromine going to an enol intermediate. The mechanism of reductive dehalogenation by second category of reagents is not settled. These reagents (alkoxides and tertiary amines) do not exhibit preference for exo or endo debromination. The third category is of radical abstraction reagents typified by tri-n-butyl tin hydride. In this debromination again there was no preference for removal of exo bromine or endo bromine. The radical abstraction mechanism for this reductive debromination may not involve movement of C-3 substituent in the transition state (i.e. a non planar radical is formed). The torsional effects would not operate and as observed there is no preference for exo or endo bromine removal.

It has not been possible to epimerise the pure 3-bromo-3-chlorocamphors by hydrogen bromide under a variety of conditions. A direct estimate of the relative stability of the two epimers could not be obtained. Indirectly by measuring rates of reductive debromination by triphenylphosphine and by bromination of chlorocamphor it was estimated that 3-exo-bromo-3-endo-chlorocamphor is $\sim$1.6 Kcal/mole less stable than the 3-endo-bromo-3-exo-chlorocamphor at 25° in 75% acetonitrile. These stabilities presumably reflect the relative magnitude of steric interactions between the C-8 methyl group and C-3 exo halogen substituent in the ground state of the ketone.

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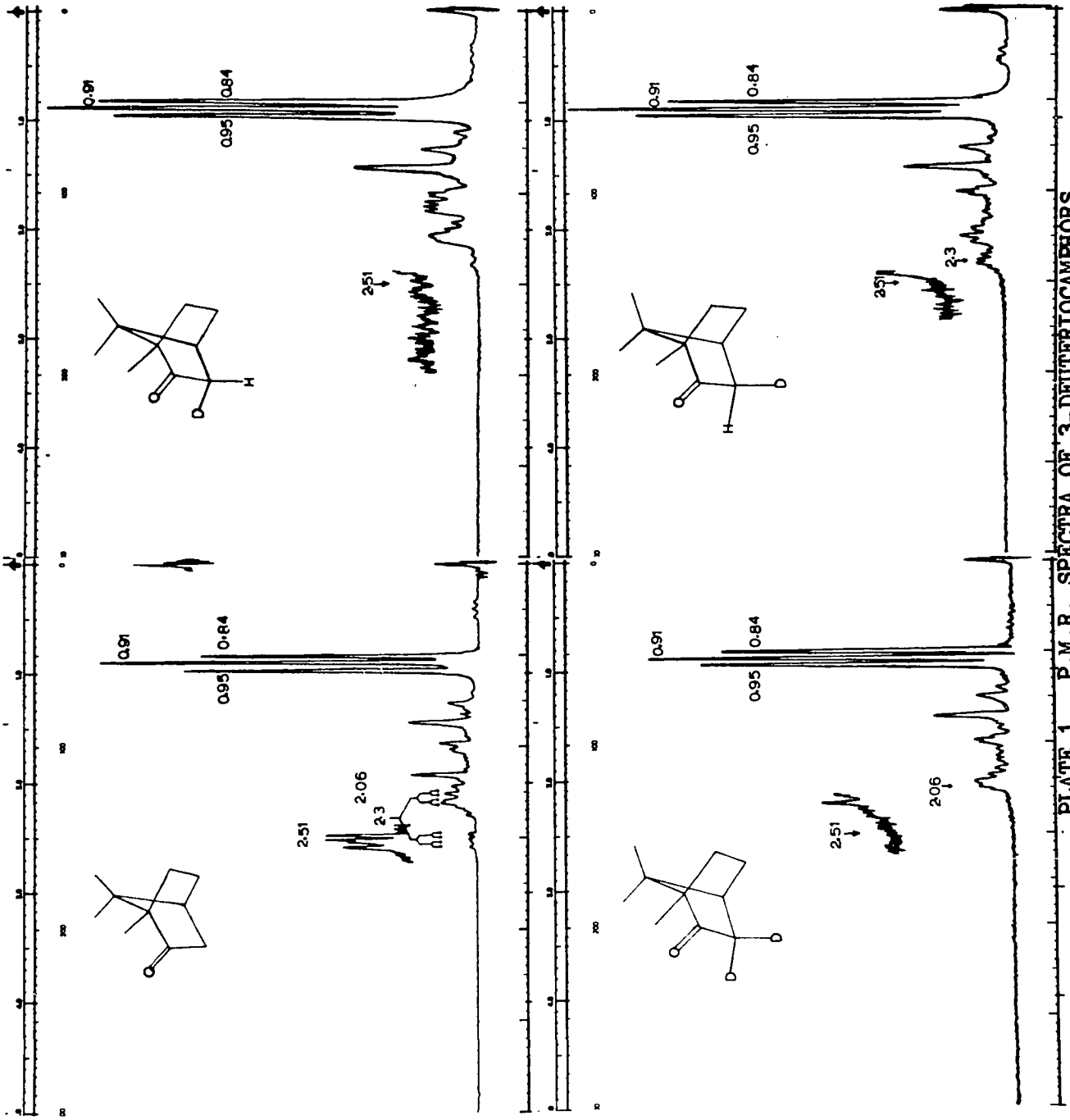


PLATE 1. P.M.R. SPECTRA OF 3-DEUTERIOCAMPHORS

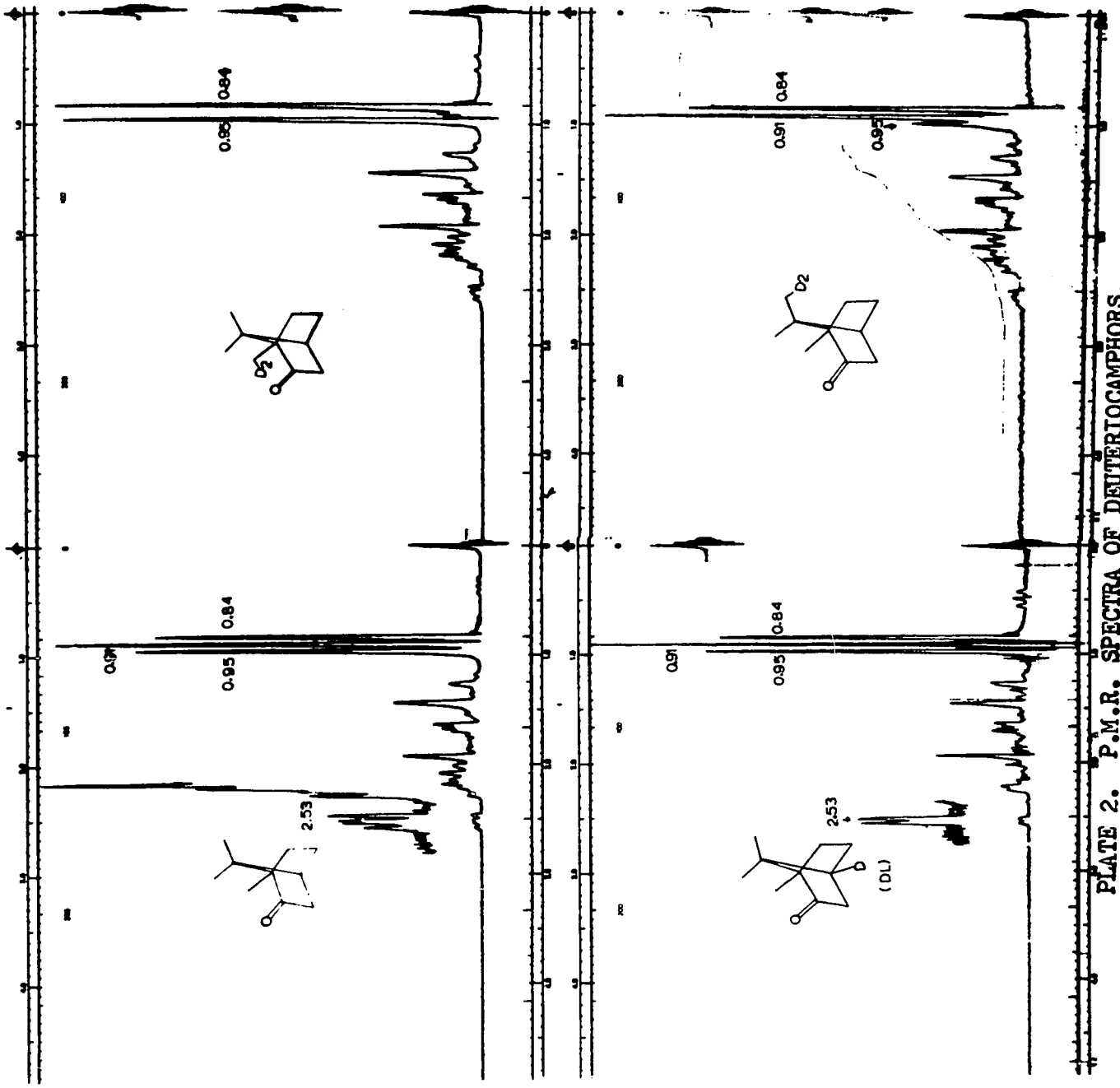


PLATE 2. P.M.R. SPECTRA OF DEUTERIOCAMPHORS.
(C-9, C-10 and C-4)

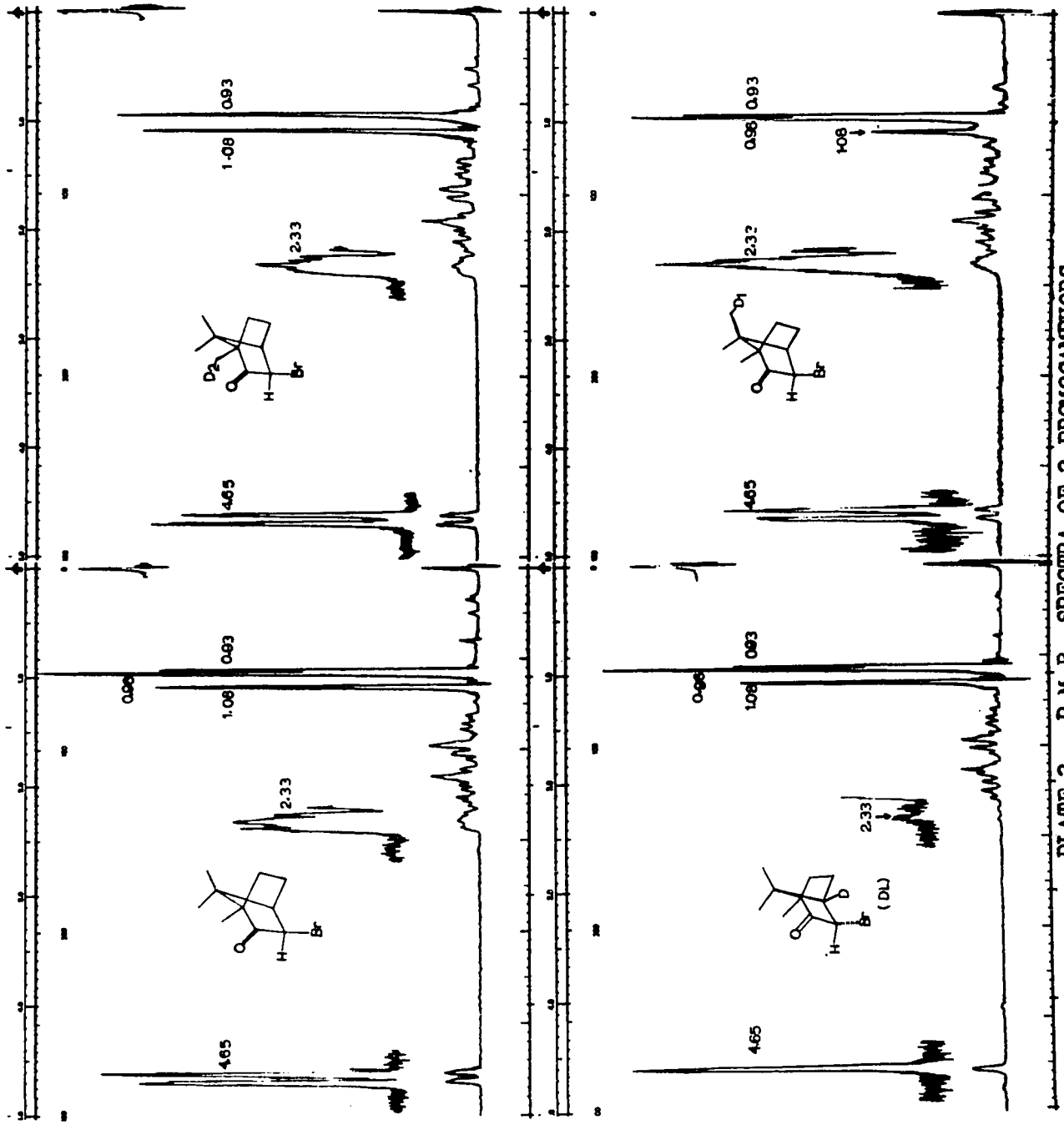


PLATE 3. P.M.R. SPECTRA OF 3-BROMOCAMPHORS

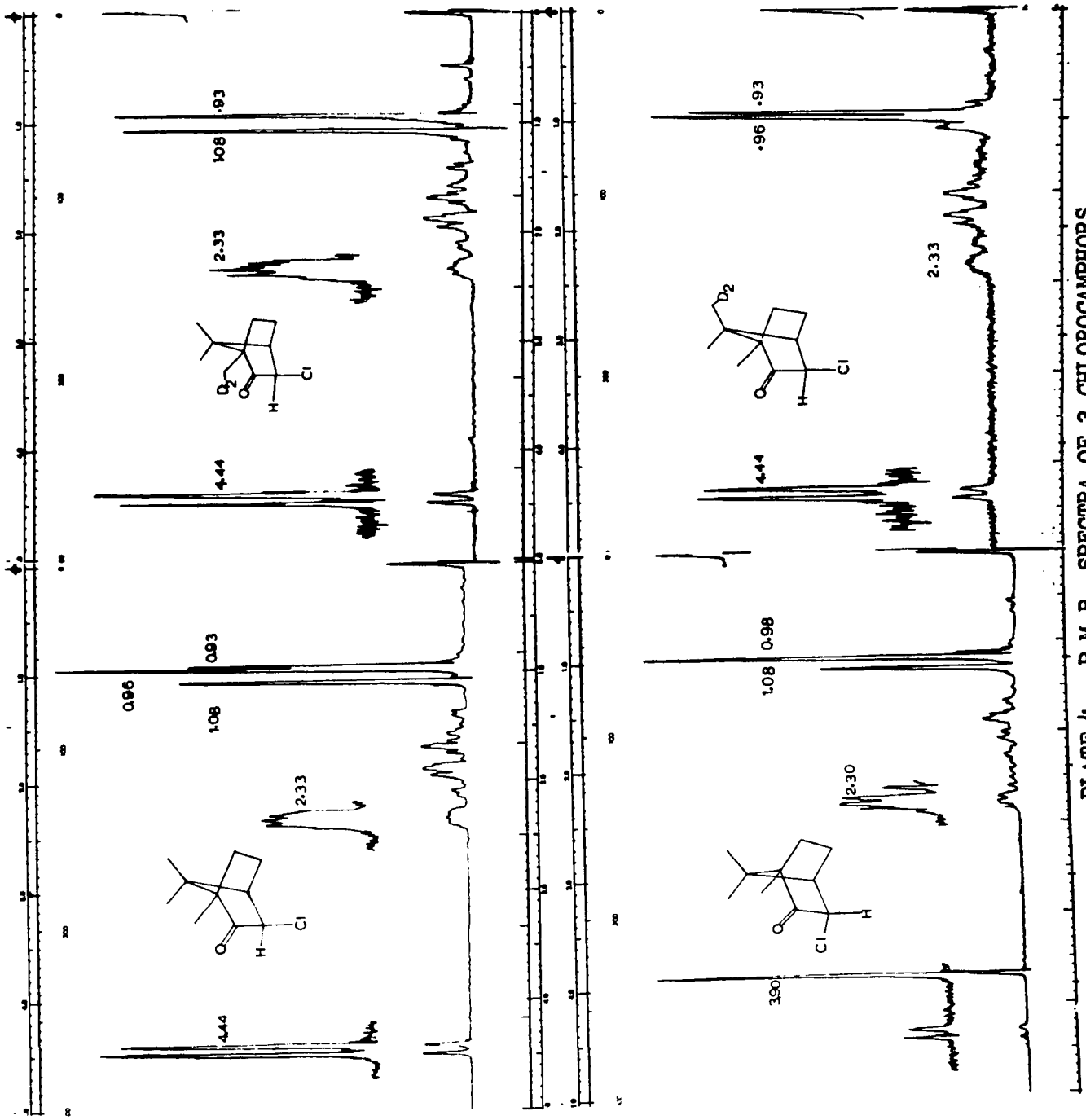


PLATE 4. P.M.R. SPECTRA OF 3-CHLOROCAMPHORS

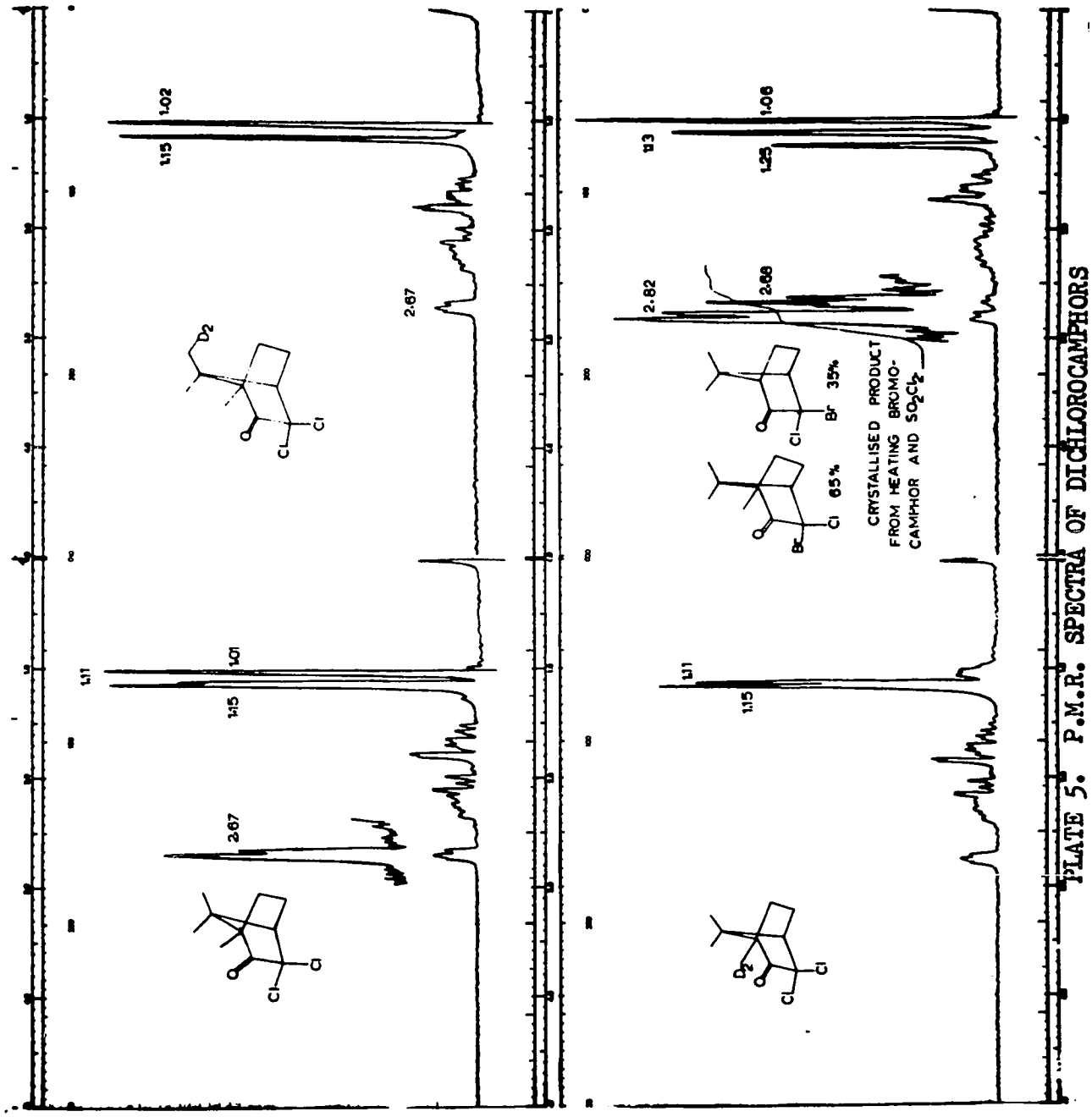


PLATE 5. P.M.R. SPECTRA OF DICHLOROCAMPHORS AND EPIMERIC BROMOCHLOROCAMPHOR

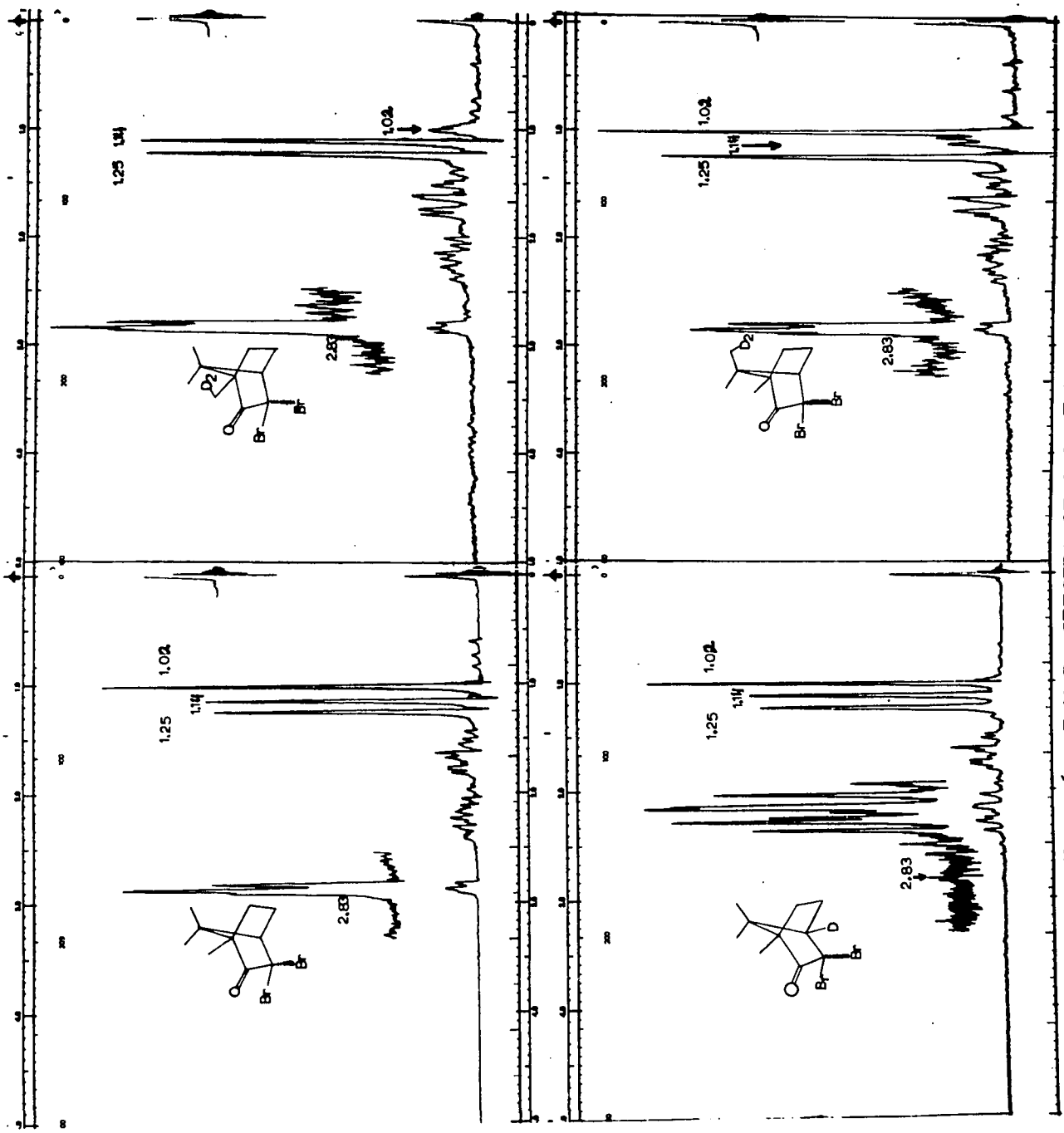


PLATE 6. P.M.R. SPECTRA OF 3,3-DIBROMOCAMPHOR

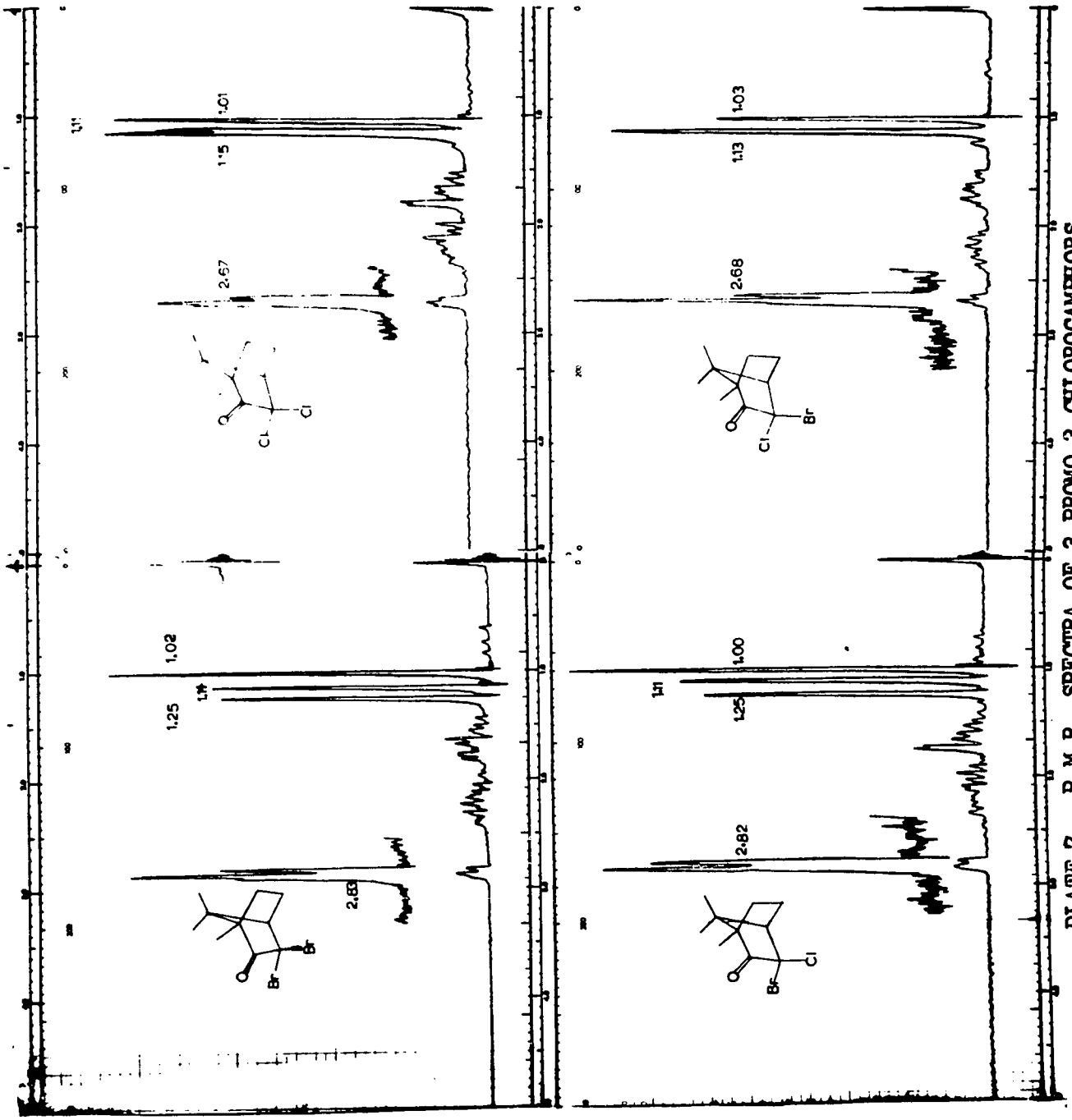


PLATE 7. P.M.R. SPECTRA OF 3-BROMO-3-CHLOROCAMPHORS

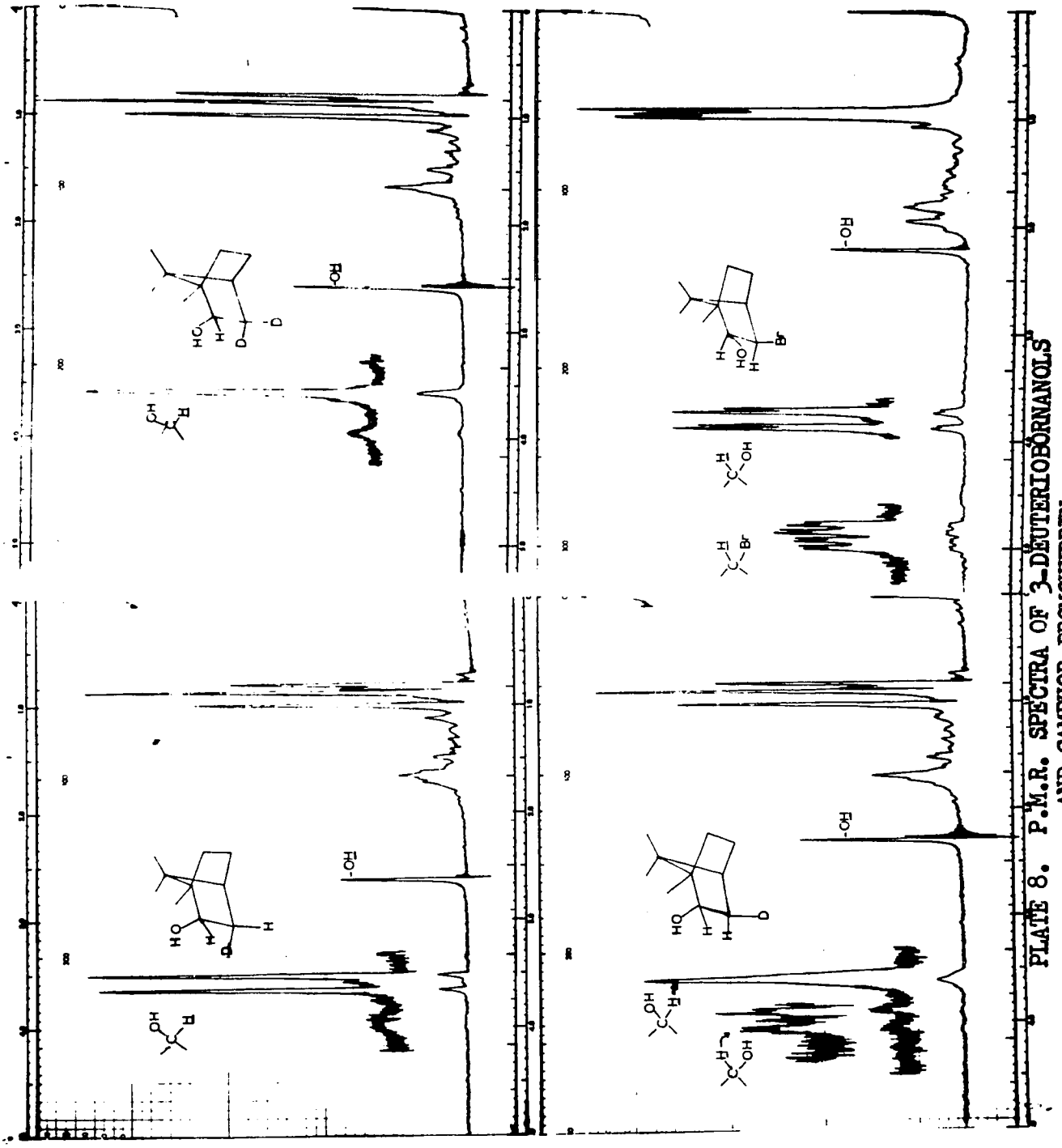


PLATE 8. P.M.R. SPECTRA OF 3-DEUTERIOBORNANOLS AND CAMPHOR BROMOHYDRIN

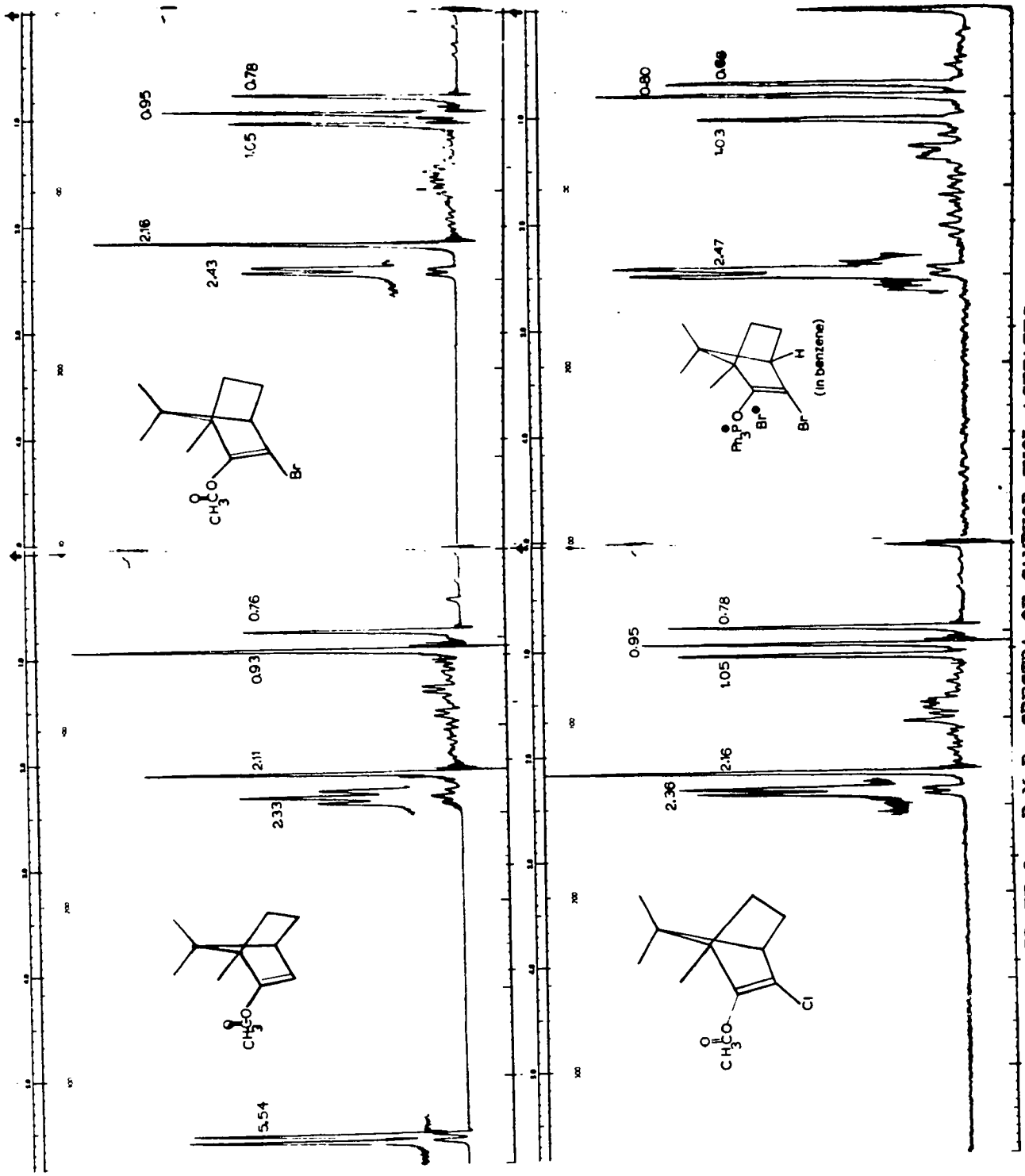
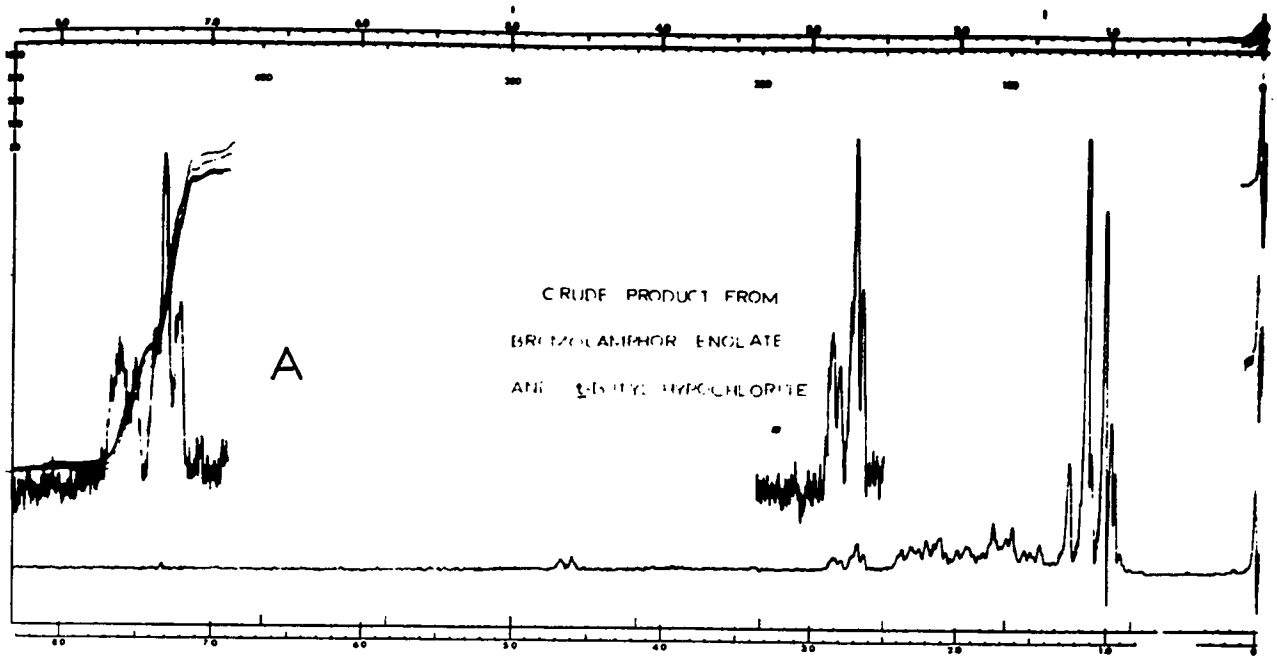
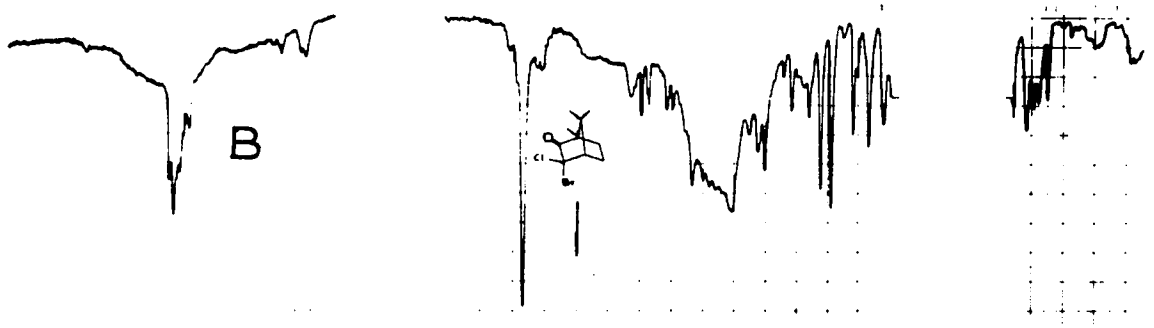


PLATE 9. P.M.R. SPECTRA OF CAMPHOR ENOL ACETATES AND BROMOCAMPHOR ENOL PHOSPHONIUM BROMIDE





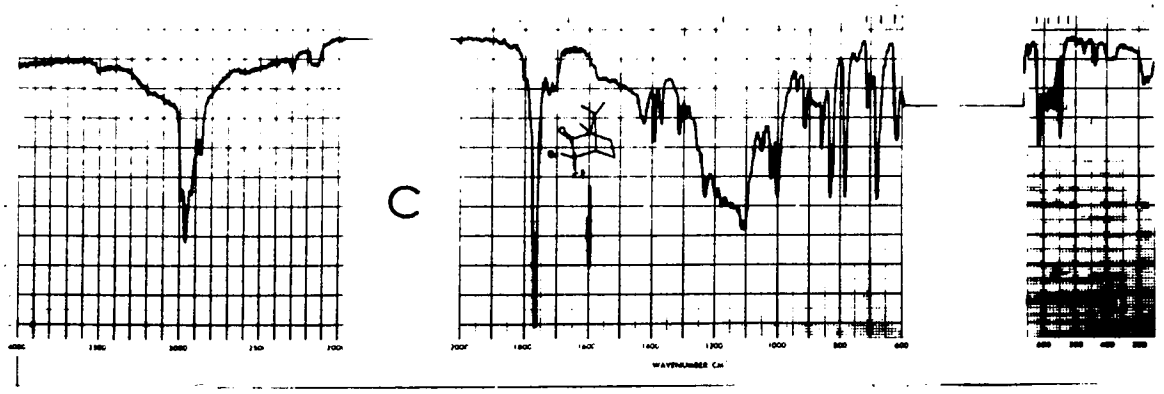
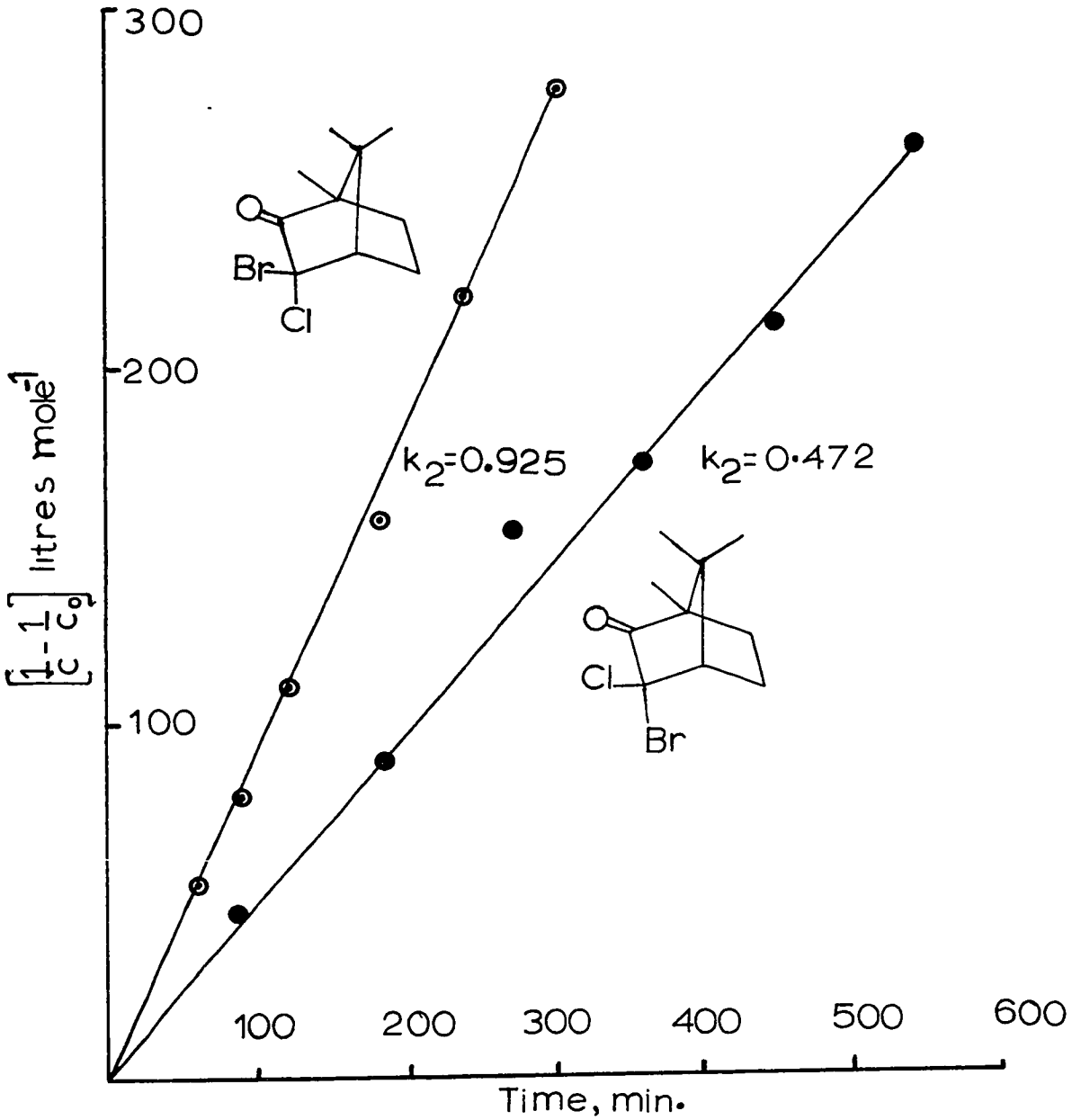


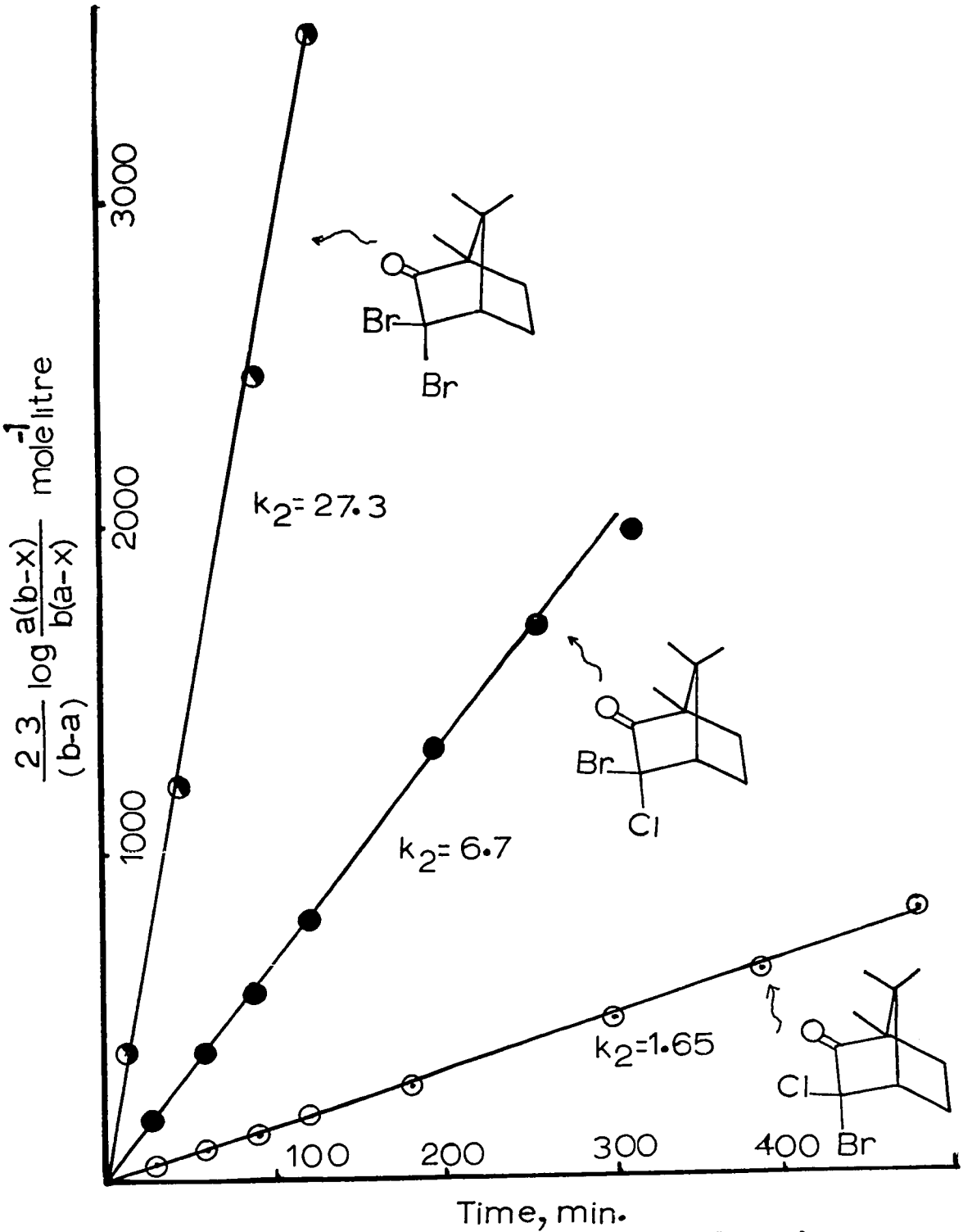
PLATE 10

A. P.M.R. spectrum of crude product obtained by chlorination of bromocamphor lithium enolate.
B. Infrared spectrum of 3-endo-bromo-3-exo-chlorocamphor.
C. Infrared spectrum of 3-exo-bromo-3-endo-chlorocamphor.



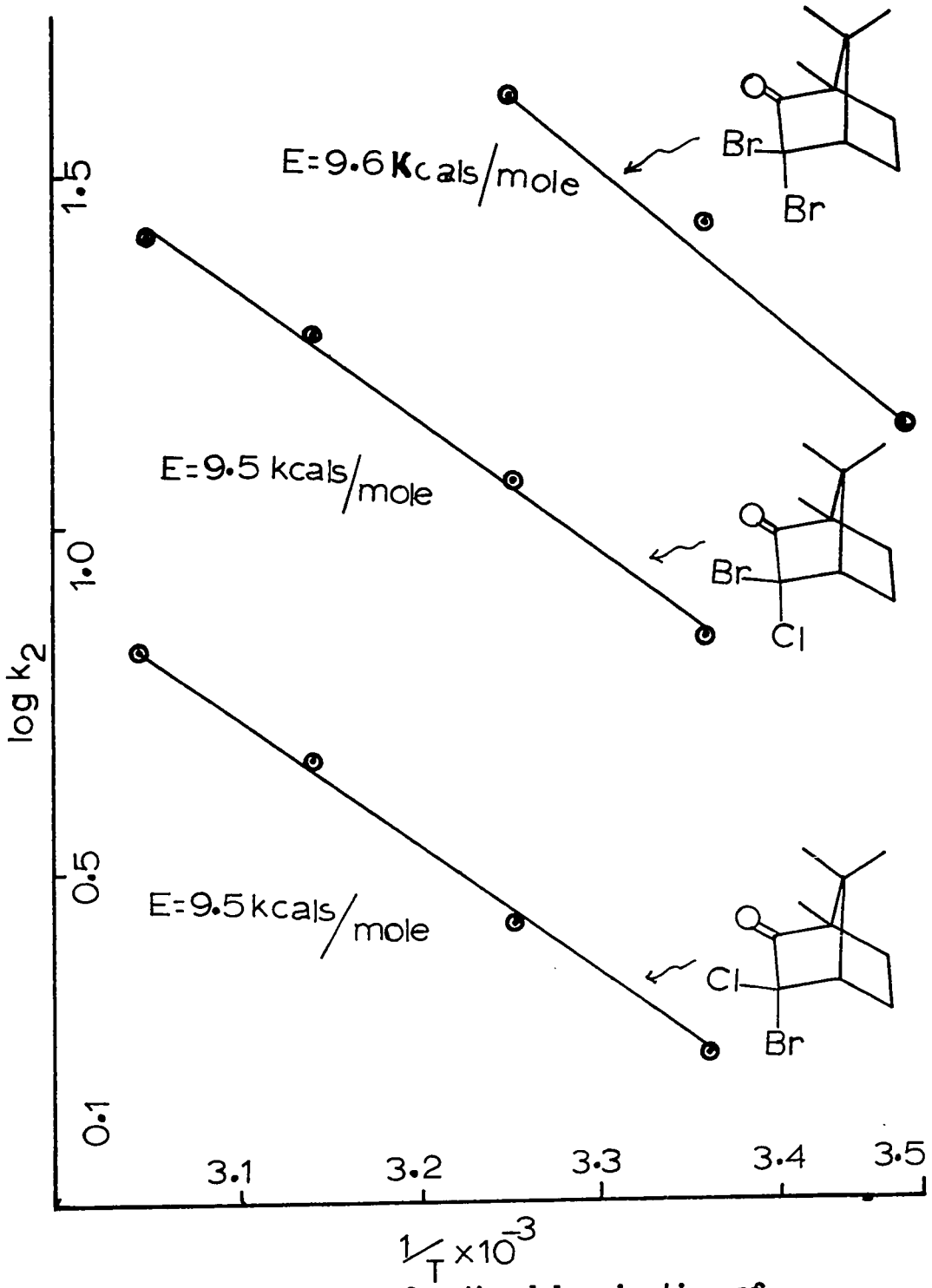
Reductive dehalogenation of epimeric dihalocamphors by triphenylphosphine in methanol at -25°.

PLATE 11



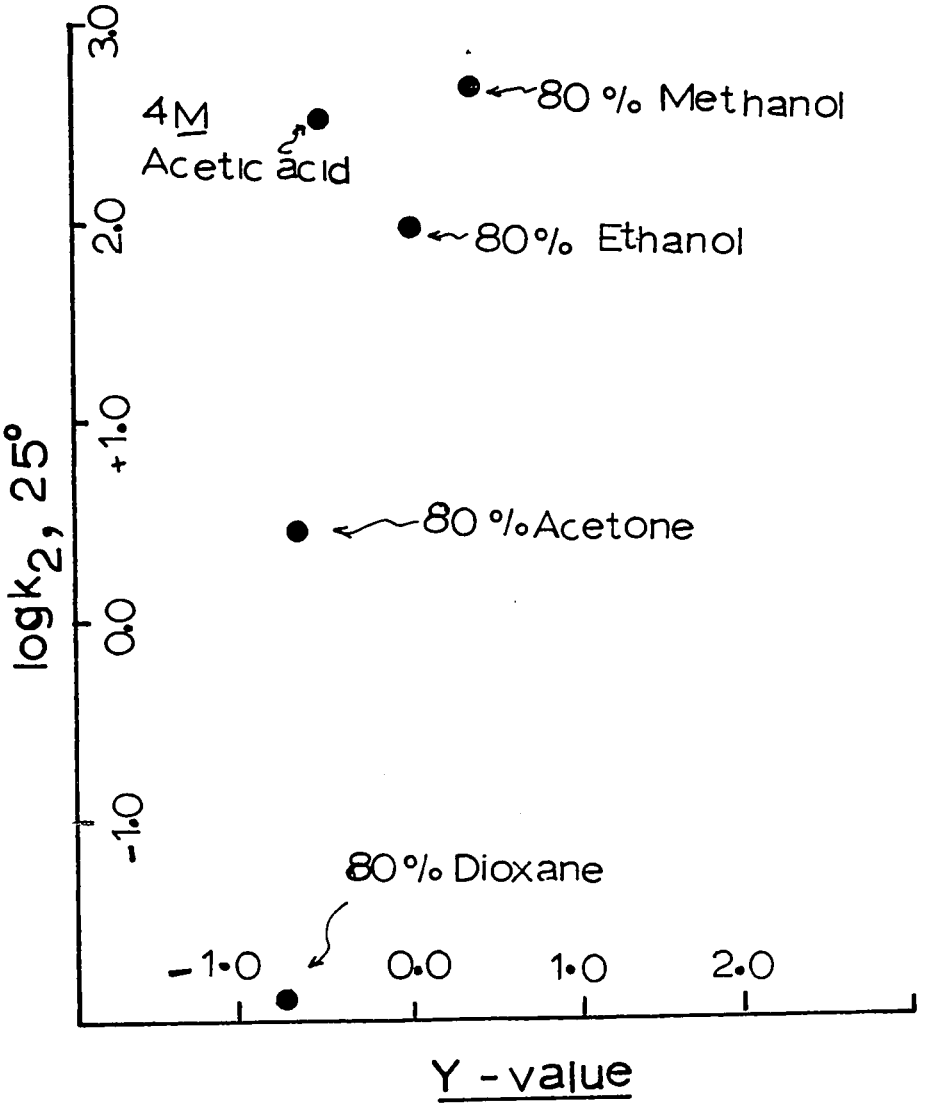
Reductive dehalogenation of 3,3-dihalocamphors by triphenylphosphine in 75% acetonitrile at 25°.

PLATE 12



Arrhenius curves for the debromination of dihalocamphors by triphenylphosphine in 75% acetonitrile.

PLATE 13



Effect of solvent polarity on the rate of debromination of dibromocamphor by triphenylphosphine at 25°.

PLATE 14

EXPERIMENTAL

GENERAL

Melting points were taken on a Reichert microscope hot stage and are corrected. Capillary melting points, where so mentioned, were taken in a Thomas Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured with chloroform solutions, unless otherwise specified, in a 1-dm tube on a Rudolph model 80 polarimeter. Infrared spectra were recorded on a Beckman IR-5A or IR-10 spectrophotometer. The ultraviolet spectra were taken on a Cary model 14 spectrophotometer. Proton magnetic resonance (PMR) spectra were determined with chloroform-d_1 solutions (30-60 mg/0.1 ml) on a Varian-A60 spectrometer at 60 Mc/s and a Varian A-100 spectrometer at 100 Mc/s.

Spin-spin decouplings were carried out on a DP-60 spectrometer. Mass spectra were run on AEI-MS9 or Varian M66 instruments.

Camag DF-5 silica gel with calcium sulfate binder was used for thin layer chromatography (TLC). Vapour phase chromatography (V.P.C.) was done on a Glowall 400 (all glass) apparatus with a 2 m column. Petroleum ether refers to a fraction boiling between 30-60°.

Standard workup procedure for extractions consisted of wash-

ing the extracts in petroleum ether or diethyl ether with water, saturated brine solution, drying over sodium or magnesium sulfate, filtration and removal of the solvent either by distillation or in a rotary evaporator at reduced pressure using a water aspirator.

3-endo-CHLORO-D-CAMPHOR

(1) D (+) Camphor (30 g, 0.2 moles) Eastman Kodak Co., $[\alpha]_D^{22^\circ}$ + 43.0° (c = 2.72, ethanol), +41.4° (c = 8.2, chloroform), m.p. 177-177.5° (capillary, on sublimed sample) in 35 ml of methanol (Fisher, spectral grade) and 1 g of mercuric chloride were taken in a 250 ml two neck flask fitted with a condenser and a chlorine inlet tube in an ice bath. Chlorine gas (Matheson) was passed for four hrs with continuous magnetic stirring. The solution turned pale yellow. Chlorine was cut off and the mass stirred with cooling for a further two hours and thereafter stored in a refrigerator overnight. The contents were taken up along with 200 ml of petroleum ether and worked up to give a white solid which was dissolved in 200 ml of ethanol, made alkaline with 5 ml of 0.2N ethanolic sodium ethoxide, refluxed briefly, neutralised with 1N hydrochloric acid and set aside in a refrigerator. A heavy white crystalline solid separated. This was collected. The crude crystals were dissolved in 150 ml of 60-80° petroleum ether, filtered hot, and the filtrate crystallised by cooling in a dry ice-acetone bath at -50° and gave 25.95 g (0.139 mole, 69.5%) of colourless cystals, m.p. 95-95.5°.

(2) D (+) Camphor (5.0 g, 33 m moles per tube) was taken in four glass tubes (i.d. 11 m.m.), and 2.7 ml (4.5 g, 33.3 m moles) of sulfuryl chloride (B.D.H., A.R.) was added to each tube, which was sealed and heated at 110° for 6 hrs. The tubes were cooled, opened, and the contents poured into 50 ml of water and extracted with diethyl ether. The crude solid obtained from the work up was dissolved in 30 ml of ethanol, made alkaline with 0.1N ethanolic potassium hydroxide, briefly refluxed, neutralised with hydrochloric

acid and crystallised by cooling, to give 18 g (from 4 tubes, 96.5 m moles, 73.4%) of colourless flaky crystals m.p. 95-95.5°. A sample recrystallised six times from ethanol was a flaky white solid, m.p. 95-95.5°, lit.[35] 94°; $[\alpha]_D^{20°}$ + 95.5° (c = 8.59, chloroform), lit.[35] $[\alpha]_D$ + 96° (ethanol); $\nu_{max}^{CS_2}$ 1758 cm^{-1} (C = O, KBr cells), lit.[41] $\nu_{max}^{CCl_4}$ 1763 (C = O); λ_{max} 303 mμ, ε 66.3 (ethanol), lit.[43] λ_{max} 305 mμ, log ε 1.72 (ethanol).

Single spot in T.L.C. (Pet. ether. - ethyl acetate, 70:30; benzene - pet. ether 50:50 systems).

P.M.R. spectrum: C-3H 4.44 p.p.m. (1H, dd), Me, 0.93, 0.96, 1.08 p.p.m. (s, 60 Mc)., C-3H 4.4 p.p.m. (1H, dd), C-4H 2.33 p.p.m. (1H, m), decoupling between 4.4 p.p.m., 2.33 p.p.m. and 1.85 p.p.m. signal (C-5HX) (100 Mc).

3-endo-BROMO-D-CAMPHOR

The directions given by Ingersall and Babcock[26] were followed. From 30.5 g (0.2 moles) of D (+) camphor and 11.5 ml (34.5 g, 0.26 moles) of bromine was obtained 38.2 g (82.5%) of crude 3-bromocamphor as white crystalline solid. A reference sample of 3-endo-bromocamphor was prepared by four recrystallisations from ethanol, m.p. 75-75.5°, lit.[135] 76-76.5°; $[\alpha]_D^{23°}$ + 133.6° (c = 4.0, ethanol), $[\alpha]_D^{19°}$ + 135.3° (c = 8.59, chloroform), lit.[29] $[\alpha]_D$ + 135° (ethanol); $\nu_{max}^{CS_2}$ 1755 cm^{-1} (C = O, KBr cells), lit.[41] $\nu_{max}^{CCl_4}$ 1758 cm^{-1} (C = O).

Single spot in T.L.C. (Pet. ether - ethyl acetate, 70:30; benzene - pet. ether 50:50 systems).

P.M.R. spectrum: C-3H 4.65 p.p.m. (1H, dd), Me 1.08, 0.96, 0.93 p.p.m. (s, 60 Mc)., C-4H 2.31 p.p.m. (1H, m, 100 Mc). Decoupling between 4.61, 2.31 and 1.83 p.p.m. signals.

3-endo-IODO-D-CAMPHOR

3-Acetoxy mercury-D-camphor (2.1 g, 5.12 mmoles) was dispersed in 25 ml of methanol and after the addition of 1.5 g of iodine the mass was stirred magnetically at room temperature for 2 hrs. The white powder dissolved and a clear pale yellow liquid resulted. This was triturated with 10 g of potassium iodide in 25 ml of water and 50 ml of petroleum ether. The aqueous layer was drained off, and the organic layer was washed thrice with 10% aqueous potassium iodide, and worked up to give 1.24 g of a clear glassy liquid, containing 55% of 3-exo-iodocamphor and 45% of 3-endo-iodocamphor. Yield of crude iodocamphor was 4.48 mmoles, 87.5%. The mass was dissolved in 10 ml of ethanol to which was added 1 ml of 1N sodium ethoxide solution, and the mixture was set aside for 48 hrs, poured in 100 ml water and extracted with petroleum ether. The residue from evaporation of the petroleum ether amounted to 1.16 g of oil (90.7% of endo epimer). Recrystallisation from petroleum ether gave leafy white crystals (turned yellow in solution on exposure to light) of pure 3-endo-iodo-D-camphor, m.p. 41-42°, lit.[135] 36-38°; $[\alpha]_D^{19.5^\circ}$ + 168.8° (c = 3.34, chloroform), lit.[135] $[\alpha]_D$ + 166° (ethanol); $\nu_{max}^{CS_2}$ 1753 cm^{-1} (C = O, KBr cells.

P.M.R. spectrum: C-3H at 5.03 p.p.m. (1H, dd), Me 1.12 (3H, s.) and 0.96 p.p.m. (6H, s).

3-FLUORO-D-CAMPHOR

D (+) Camphor (7.8 g, 51 mmoles) in 200 ml of dry tetrahydrofuran under nitrogen was treated with 38 ml of 1.6M (61 mmoles) n-butyllithium at room temperature for 30 min. The solution (pale clear liquid) was poured on ~100 g of powdered solid carbon diox-

ide. After the lumps of dry ice disappeared, the residue was dissolved in water and extracted with diethyl ether. The ether extract (mostly camphor) was rejected. The aqueous extract was acidified cautiously with 1:1 hydrochloric acid in the cold till strongly acidic (pH~1.0). The liberated organic acid was extracted with 300 ml of diethyl ether in 3 portions, the ether solution was worked up to give a white sticky mass which tended to crystallise and yielded 9.2 g (46.8 mmoles, 92%) of camphor-3-carboxylic acid, m.p. 120-125° on crystallisation from ether. The crude acid (6.5 g, 33 mmoles) was kept in 20 ml of thionyl chloride solution at room temperature for 4 hrs and mildly refluxed for 2 hrs. Excess thionyl chloride was distilled off on the steam bath to leave a residue of 7.03 g of pale yellow liquid. The crude acid chloride was treated with 20 ml of absolute ethanol and 5 g of dry potassium bicarbonate with magnetic stirring in an ice bath for 1 hr. Water (50 ml) was added and stirring continued for another hr. The mixture was extracted with 3 x 50 ml of diethyl ether, the ether solution was washed once with saturated bicarbonate solution and worked up to give 6.73 g (30 mmoles, 91% on crude acid) of pale yellow oily 3-carbethoxy camphor epimers. P.M.R. spectrum: $-OCH_2$ 4.0 p.p.m. (m), C-4H 2.91 p.p.m. (m).

The crude carbethoxy camphor (6.7 g, 30 mmoles) in 100 ml of dry tetrahydrofuran was treated with 20 ml of 1.6M (32 mmoles) n-butyllithium under nitrogen. Perchloryl fluoride (Pennsalt chemicals) was bubbled with stirring. Considerable heat evolved and the initially deep red-brown solution turned light yellow.

Nitrogen was bubbled vigorously to flush off excess reagent, the mass diluted with 100 ml of diethyl ether, filtered and filtrate evaporated. The 6.9 g of residual oily brownish solid was refluxed with a solution of 20 ml of water, 4 g of sodium hydroxide and 30 ml of methanol for 1 hr. After cooling the mixture was diluted with 100 ml of water and extracted with petroleum ether to yield 5.5 g of oily solid. The P.M.R. spectrum showed ~30% of fluorocamphor and the rest camphor. Slow sublimation at atmospheric pressure gave two zones, a front zone (light feathery crystals) was camphor followed by a light creamy crystal of fluorocamphor, free of camphor. P.M.R. spectrum had C-3 HX at 4.87 p.p.m. (m, J3HX, 3F = 54 c.p.s., J3HX, 4 H = 5 c.p.s., J3HX5HX = 1 c.p.s., intensity 56%) and C-3HN at 4.4 p.p.m. (J3HN, 3F = 53 c.p.s., intensity 44%).

Crude 3-fluorocamphor (2.3 g, 13.5 mmoles) was dissolved in 50 ml of tetrahydrofuran in the reactor (reverse addition assembly) under nitrogen. n-Butyllithium (12 mls of 1.6M, 19.2 mmoles) was injected. After 30 min. the light yellow solution of enolate was added dropwise to a stirring solution of 10 ml of acetic acid (~ 10 g, 160 mmoles) in 50 ml of water. The mixture was extracted with petroleum ether, and worked up to give 2.25 g of yellow oil.

P.M.R. spectrum: C-3HX 4.87 p.p.m. (ddd), 90.5% (3-endo-fluorocamphor) C-3HN 4.4 p.p.m. (d) 9.5% (3-exo-fluorocamphor). Me 1.05, 0.94, 0.90 and 0.86 p.p.m. (s). There was an unidentified doublet at 4.23 p.p.m. (J = 56 c.p.s.).

3,3-DIBROMO-D-CAMPHOR

The directions given by T.M. Lowry[36] were followed. From 23.1 g (100 mmoles) of 3-endo-bromo-D-camphor (Eastman Kodak) was obtained 27.8 g (89.5%)of crude 3,3-dibromocamphor as a white crystalline solid. A second crystallisation from methanol and one crystallisation from petroleum ether gave 25.9 g of shining white needles, m.p. 58.5-59.5°, lit. 60°; $[\alpha]_D^{20°}$ + 38.01° (c = 4.5, ethanol), 39.8° (c = 8.16, chloroform), lit.[36] $[\alpha]_D$ + 40° (ethanol); $\nu_{max}^{CS_2}$ 1763 cm^{-1} (C = O, KBr cells), lit.[41] $\nu_{max.}^{CCl_4}$ 1766 cm^{-1} (C = O); λmax 317.5 mμ, ϵ = 90.5 (ethanol), lit.[43] λ_{max} 310 mμ, log ϵ 1.82.

P.M.R. spectrum: C-4H 2.83 p.p.m. (1H, m), Me 1.25, 1.14 and 1.02 p.p.m. (s).

3,3-DICHLORO-D-CAMPHOR

(1) Based on the directions given by Lowry[36] from 3.72 g (20 mmoles) of 3-endo-chlorocamphor and 2.2 ml (25 mmoles) of sulfuryl chloride at 120° for 4 hrs in a sealed tube and after workup was obtained 3.61 g of a crude product containing traces of 3-chlorocamphor. A reference sample was prepared by four recrystallisations from methanol to give 1.56 g (35%) of 3,3-dichloro-D-camphor as small white needles, m.p. 94.5 -95.5°, lit.[36] 96°; $[\alpha]_D^{20°}$ + 58.96° (c = 8.1, chloroform), lit.[36] $[\alpha]_D$ + 57.3° (ethanol); $\nu_{max}^{CS_2}$ 1773 cm^{-1} (C=O, KBr cells), lit.[41] $\nu_{max}^{CCl_4}$ 1774 cm^{-1} (C=O); λmax 310 mμ, ϵ 41.5 (ethanol), lit.[43] λmax 310 mμ, log ϵ 1.82.

P.M.R. spectrum: C-4H 2.67 p.p.m. (m), Me 1.15, 1.11, 1.02 p.p.m. (s).

(2) 3-Chlorocamphor enol acetate (4.36 g, 19 mmoles) was taken in 10 ml of carbon tetrachloride in a 250 ml flask. A crystal of iodine and 16 ml of a 1.3 M chlorine solution (in carbon tetrachloride) was added. The flask was stoppered and the contents stirred magnetically for 10 hrs at room temperature. The solvent and by product acetyl chloride were removed in a rotary evaporator leaving 4.182 g of oil which crystallised on cooling. Two recrystallisations from methanol gave 3.62 g (16.3 mmoles, 86%) of white crystalline needles, m.p. 95-95.5°.

3-exo-BROMO-D-CAMPHOR

Preparation is based on Lowry's procedure[29]. In a typical preparation 20 g of 3-endo-bromo-D-camphor was dissolved in 10 ml of ethanol to which 3 ml of 0.1N methanolic sodium methoxide was added and the mixture boiled for 10 min. The mass was cooled, neutralised with 0.1N hydrochloric acid (to pH ~ 4.0), solvent removed under vacuum, the residue dissolved in methylene chloride, filtered, and evaporated. The residue was taken up in 20 ml of methanol, chilled in a dry ice acetone bath and filtered quickly under suction. The filtrate was evaporated and rotation determined in an aliquot, $[\alpha]_D$ + 80° (c = 4, ethanol). One more fractionation from methanol followed by two further fractionations from ethanol-petroleum ether mixture gave a filtrate which after removal of solvent had $[\alpha]_D^{25°}$ + 18.2° (c = 5, ethanol). The total recovery was 0.242 g (1.2%).

T.L.C. on silica gel plate (benzene: chloroform, 1:1) single spot, Rf. same as for 3-endo-bromo-D-camphor.

P.M.R. spectrum: C-3H 4.08 p.p.m. (s), Me 1.14 p.p.m. (3H, s)

and 0.97 p.p.m. (6H, s) at 60 Mc . C-3H at 4.02 p.p.m. (s), C-4H 2.35 p.p.m. (d) at 100 Mc. Composition ~ 70% 3-exo-bromo-D-camphor, rest 3-endo-bromo-D-camphor.

3-exo-CHLORO-D-CAMPHOR[29]

3-endo-Chloro-D-camphor (20 g) was dissolved in 20 ml of ethanol, 3 ml of 0.1 N sodium methoxide in methanol added and the solution refluxed for 10 min. After cooling it was neutralised with 0.1N hydrochloric acid, cooled in a dry ice acetone bath, filtered quickly under suction and filtrate set aside. The residue on the sintered funnel was dissolved again in 20 ml ethanol, 3 ml 0.1N sodium methoxide solution added, mixture refluxed, cooled and filtered under suction. This operation was repeated 6 times and the combined filtrate was evaporated under suction, leaving 5.4 g solid. This was dissolved in 10 ml ethanol, chilled in dry ice acetone bath and filtered quickly. The filtrate was again cooled, filtered under suction to separate any crystallised solid and the operation was repeated 10 more times. The filtrate was evaporated leaving, 202 mg (~ 10%) solid, $[\alpha]_D^{22^\circ}$ + 30° (c = 4.2, ethanol).

T.L.C. (benzene, chloroform 1:1) single spot, Rf. identical with that of 3-endo-chloro-D-camphor.

P.M.R. spectrum C-3H 3.9 p.p.m. (s), Me 1.08 p.p.m. (3H, s) and 0.97 p.p.m. (6H, s) (60 Mc). (70% 3-exo-chlorocamphor). C-3H 3.86 p.p.m. (s) and C-4H 2.27 p.p.m. (d) (100 Mc).

D-CAMPHOR QUINONE

The preparation was based essentially on the procedure of Evans, et al.[136] From 20.04 g (130 mmoles) of D-camphor was obtained

17.99 g (83% of D-camphor quinone as bright wooly crystals, m.p. 197-197.5° (from pet. ether), lit.[136] 198°; $\nu_{max}^{CS_2}$ 1754, 1775 cm^{-1} (C=O).

P.M.R. spectrum: C-4H 2.63 p.p.m. (m), Me 1.09, 1.07 and 0.91 p.p.m. (s).

A milligram scale preparation (useful for characterising C-4 and C-5 deuterio camphors) typically used 42.5 mg of D (+) camphor, 87 mg of selenious acid, 0.05 ml of acetic acid (90% acid - 10% water) in a sealed tube heated for four hrs at 150°. A yellow solution with suspended black solid resulted. The tube was cooled, opened and the contents poured into sodium bicarbonate solution. After several extractions with diethyl ether the combined ether solutions were worked up to give 44 mg (94.5%) of yellow wooly residue. Recrystallised from 60-80° pet. ether yellow fibres, m.p. 197-198°.

DIAZOCAMPHOR

Camphor quinone (10.03 g, 60 mmoles) was converted to its monohydrazone in 87% yield (procedure of Bredt and Holtz[137]). The crude monohydrazone (8.14 g, 45 mmoles) was treated with 12.4 g (57.5 mmoles) of "red" mercuric oxide in 70 ml of benzene according to the directions of Bredt and Holtz[138] to give 7.45 g (93.5%) of diazocampnor as large yellow crystals from 60°-80° pet. ether, m.p. 73.5-74°, lit.[138] 74-75°; $\nu_{max}^{CS_2}$ 1695 (C = O), 2080 cm^{-1} (N≡N).

P.M.R. Spectrum: C-4H 2.95 p.p.m. (1H, d, J = 3 c.p.s.), Me 1.0, 0.97, 0.93 p.p.m. (s).

3,5-CYCLO-D-CAMPHANONE

A solution of 6.213 g (35 mmoles) of diazocamphor in 50 ml of freshly distilled diglyme was added during 2 hrs through a dropping funnel to a suspension of 10 g of copper powder (electrolytic, Fisher) in diglyme, stirred and heated at ~140°. After cooling the mass was filtered under suction, poured into a large excess of water and extracted with petroleum ether. Evaporation of the solvent left an oily semi solid. This was chromatographed on 200 g of neutral alumina (grade IV) and eluted with petroleum ether. Evaporation of the eluate left 3.39 g (22.6 mmoles, 64%) of white solid D-cyclocamphanone. A reference sample was prepared by sublimation, m.p. 167-168°, lit.[138] 166-168°; $\nu_{max}^{CS_2}$ 1752 (C = O), 3035 cm^{-1} (Δ_H). Characteristic five lines between 800-900 cm^{-1}.

P.M.R. Spectrum: Me 0.97, 0.88, 0.78 p.p.m. (s).

(The yields of pure 3,5-cyclocamphanone varied between 60-70% in this procedure).

3-BROMO AND 3-CHLORO-3,5-CYCLO-D-CAMPHANONES

3,5-cyclo-D-Camphanone (695 mg, 4.6 mmoles), 10 ml of acetic acid, 2 ml of constant boiling hydrobromic acid and 1 g of lithium bromide were heated on a water bath under a condenser for 4 hrs. The mixture was cooled, poured on ice, carefully neutralised with cold aqueous sodium hydroxide solution and extracted with diethyl ether. The ether extract after work up gave 1.042 g (4.5 mmoles, 98%) of 5-exo-bromo-D-camphor as a feathery solid. The reference sample was sublimed, m.p. 110-110.5°, lit.[135] m.p. 111-111.5°; $\nu_{max}^{CS_2}$ 1745 (C = O), 880 and 600 cm^{-1} (KBr cells).

P.M.R. spectrum C-5H at 4.05 p.p.m. (1H, m), C-4H 2.5 p.p.m. (1H, d, J = 5 c.p.s.), Me 1.37, 0.94, 0.86 p.p.m. (s).

From an independent preparation 1.225 g (5.3 mmoles) of 5-exo-bromo-D-camphor and 780 mg (5.8 mmoles) of sulfuryl chloride were heated in a sealed tube at 112° for 14 hrs. The tube was cooled, opened, the contents taken up in petroleum ether, and worked up to give 1.315 g (4.95 mmoles, 93.7%) of two 3-chloro-5-exo-bromocamphors epimeric at C-3 as a solid.

P.M.R. spectrum 4.7 p.p.m. (1H, m J5HN, 6HN 8 c.p.s., J5HN, 6HX 6 c.p.s.), 4.43 p.p.m. (1H, d, J3HX, 4H 5 c.p.s.), Me 1.46 p.p.m. (3H, s) and 0.98 p.p.m. (6H, s). Analytical sample was prepared by sublimation, m.p. 80-83°.

Anal. Cal. for $C_{10}H_{14}OBrCl$ (265.6) C, 45.2; H, 5.27; Br, 30.1; Cl, 13.4.

Found C, 45.66; H, 5.16; Br, 29.9 and Cl 13.1.

3-Chloro-5-exo-bromo-D-camphor (1.1011 g, 4.15 mmoles) was refluxed with 20.5 ml of 0.25 N sodium ethoxide in ethanol for 2 hrs. The mass was cooled, poured in water and extracted with petroleum ether. The residue after work up amounted to 705 mg of highly volatile solid 3-chloro-3,5-cyclo-D-camphanone, m.p. 58.5-59.5°, $\nu_{max}^{CS_2}$ 1780 cm.$^{-1}$ (C = O, KBr cells), $[\alpha]_D^{19°}$ + 40.6° (c = 2.04, ethanol).

P.M.R. spectrum: Me 0.97 p.p.m. (6 H, s) and 0.88 p.p.m. (3H, s).

Anal. calculated for $C_{10}H_{13}OCl$ (184.7) Cl, 19.41.

Found Cl, 18.54.

5-exo-Bromo-D-camphor (1.52 g, 6.7 mmoles) and 2.875 g of Fisher bromine charcoal reagent (40% available bromine, 1.15 g, 7 mmoles) were heated in a sealed tube along with a drop of fuming

hydrobromic acid, at 105-106° for 12 hrs. After cooling and opening of the tube the residue was extracted with petroleum ether, and worked up to give 1.491 g (4.8 mmoles, 71.5%) residue which was sublimed, m.p. 55-60°, lit.* 58-59° for 3,5-dibromoc amphor. P.M.R. spectrum: 4.76 p.p.m. (1H, m), 4.7 p.p.m. (1H, m), C-4H at 2.7 p.p.m. (1H, d J = 5 c.p.s.), Me 1.46 p.p.m. (3H, s), 1.0 p.p.m. (6H, s).

The 3,5-dibromocamphor (1.43 g, 4.6 mmoles) was refluxed with 10 ml of 1N sodium ethoxide in ethanol for 4 hrs and worked up as in the case of 3-chloro-5-bromocamphor. The residue from the petroleum ether amounted to 990 mg (93%) of 3-bromo-3,5-cyclocamphanone, which was sublimed, m.p. 70-70.5°, $\nu_{max}^{CS_2}$ 1780 cm^{-1} (KBr cells), $[\alpha]_D^{19°}$ + 29° (c, 3.17, ethanol).

P.M.R. spectrum: Me 0.97 p.p.m. (6H, s) 0.9 p.p.m. (3H, s)

Anal. Calcd. for $C_{10}H_{13}OBr$ (229.12) C, 52.4; H, 5.67; Br, 35.0.

Found C, 52.61; H, 5.67; Br 34.84.

D-CAMPHOR-10-SULFONYLCHLORIDE

Calcium carbonate (50 g, Malinckrodt, Powder, A.R.) and 100 ml of thionyl chloride (Fisher, freshly distilled) were swirled manually in a 1 l. round bottom flask. D-Camphor-10-sulfonic acid (Aldrich chemicals), 50 g (215 mmoles) was added while the flask was swirled gently. After adding all the acid the mixture was refluxed gently for 4 hrs. The condenser was removed and unreacted thionyl chloride distilled off. The potresidue was cooled, 50 ml of 60-80° petroleum ether was added and then distilled off to flush out residual thionyl chloride. The residue

* Ref. 20, p. 417.

was dissolved in 500 ml of dry diethyl ether and filtered through a sintered glass funnel. The residue on the funnel was washed with 100 ml of diethyl ether. After all the ether had been distilled from the filtrate on a water bath the clear colourless liquid remaining crystallised on cooling to yield 48.5 g solid. Recrystallisation from 60-80° petroleum ether gave 45.2 g (180 mmoles, 83%) of white flaky crystals, m.p. 66-66.5°, lit.[59] m.p. 67-68° for D-camphor-10-sulfonyl chloride.

D-CAMPHOR-10-CHLOROSULFOXIDE

p-Toluenesulfonyl chloride (B.D.H., 38.2 g, 200 mmoles) and 40 ml of pyridine (Fisher) were taken in a three neck 1 l. flask fitted with a stirrer, dropping funnel and a condenser set over a steam bath. The contents were heated till the internal temperature was 90-92° and was maintained in this region. D-Camphor-10-sulfonyl chloride (50 g, 200 mmoles) was dissolved in 30 ml of hot dioxane and taken in the dropping funnel. This solution was added dropwise with stirring over a period of 45 min. Stirring was continued for another hour. The mixture was cooled to ~ room temperature and 600 ml of dry diethyl ether was run in with vigorous stirring. A lumpy solid separated and stuck to the side of the flask. After stirring under reflux for 30 min, the hot ether layer was decanted and filtered. The filtrate was distilled. The residue was dissolved in 300 ml of vigorously boiling 80-100° petroleum ether and allowed to crystallise in a refrigerator. Light pinkish yellow crystals were formed and collected, to give a first crop of 30.5 g, m.p. 84.5-85°. The filtrate was concentrated to ~75 ml and cooled again. A second crop of crystals was also collected as before, 8.5 g, m.p. 84.5-85°. The

two crops were combined for a total recovery of 39.0 g (85.5%) D-camphor-10-chlorosulfoxide, lit.[60] m.p. 85-86°.

P.M.R. spectrum: Me at 1.13 p.p.m. (6H, s.).

D-CAMPHOR-10-THIOL-10, 10-d_2

In a typical run 15 g of aluminium powder (aluminium metal granular, < 20 mesh. Fisher.) was taken in a 500 ml three neck flask. Mercuric chloride, 1 g, dissolved in 100 ml of dry tetrahydrofuran was poured over the aluminium powder. The mass was swirled for 2 min and the resulting dark grey solution was carefully decanted. The residual mass of aluminium amalgam was repeatedly washed with 200 ml (total) tetrahydrofuran by swirling and decanting till the supernatant was no more than slightly hazy. Dry tetrahydrofuran (200 ml, freshly distilled over lithium aluminium hydride) was added and the flask on a steam bath was fitted with a condenser, a mechanically driven stirrer (Teflon blade) and a dropping funnel. The contents of the reaction were protected from moisture by calcium chloride tubes on the condenser and dropping funnel. The stirrer was started and 10 g (43 mmoles) of D-camphor-10-chlorosulfoxide was added in one lot while the mass was still at room temperature. Deuterium oxide (10 ml, > 98% isotopically pure) was dissolved in 50 ml of dry tetrahydrofuran, and the solution added dropwise with stirring during 30 min. The contents were then refluxed with stirring for 4 hrs. A further 100 mg of mercuric chloride was added and resulted in a vigorous reaction. More deuterium oxide (5 ml) was run in dropwise. Reflux with stirring was continued for another 6 hr period. The hot material was filtered, and the filtrate was

distilled on a steam bath. A white crystalline solid remained, and was 7.744 g (41.5 mmoles, 96.5%) of D-camphor-10-thiol-10-d_2. This was recrystallised from petroleum ether, m.p. 65.5-66°, lit.[139] 66° for D-camphor-10 thiol. The crystalline material had only a faint odour of mercaptan.

P.M.R. spectrum: Me 1.03 and 0.91 p.p.m.

D-CAMPHOR-10-d_2

(a) Raney nickel procedure - D-Camphor-10-thiol-10-d_2 (3.71 g, 20 mmoles) was dissolved in 100 ml of absolute ethanol, approximately 40 g of W4-Raney nickel in ethanol was added. The contents were stirred while vigorously refluxing on a steam bath for 10 hrs. The flask was cooled, the contents filtered under suction, and the residue in the flask rinsed with 20 ml ethanol and filtered. The combined filtrates were distilled to approximately 10 ml. The residual solution was poured into 100 ml of water and extracted with petroleum ether (3 x 25 ml). The combined ether extracts were dried over sodium sulfate, filtered and solvent distilled on a steam bath to leave 2.25 g (73%) of white solid camphor-10-d_2. After further purification by sublimation the m.p. of the sublimate was 177-177.5° (sealed capillary). Recovery 1.10 g.

P.M.R. spectrum: Me at 0.95, 0.84 p.p.m. (s). Residual signal from $-CD_2H$ at 0.91 p.p.m.

Deuterium analysis from Mass spec. gave 84.5% camphor-d_2, 12.8% d_1 and 2.7% d_o. The major peaks in the mass spec. were m/e 154, 139, 110, 97, 95, 83 and 71.

(b) Nickel boride procedure - Following the directions of

Truce and Perry[64], 7.29 g (39 mmoles) of D-camphor-10-thiol-10-d_2, 200 ml of absolute ethanol and 92.5 g of nickel^{II} chloride hexahydrate (B.D.H.) were placed in a 1 l. 3-neck flask fitted with a stirrer, a condenser and a dropping funnel, in a salt-ice bath. Nitrogen was introduced through the dropping funnel for twenty min with stirring. Nitrogen was cut off, and 44.5 g of sodium borohydride dissolved in 100 ml of cold water was added dropwise to the stirring ethanol solution at a rate which did not cause excessive frothing.* After addition was complete ($\sim$2 hours) the mass was allowed to attain room temperature slowly ($\sim$1.5 hrs). The ice bath was replaced by a steam bath, the contents were brought to active reflux for 8 hrs. The mass was cooled and filtered, and the residue on the filter washed with ether. The combined ethanol - ether filtrates were poured into 2 l. of cold water, and extracted in three fractions, each time using 3 x 100 ml of diethyl ether. Combined ether extracts were worked up to give 4.2 g (70%) of white solid camphor-d_2. Infra red and P.M.R. spectra on the crude product indicated slight reduction of the carbonyl group.

3-BROMO-D-CAMPHOR -9-SULFONIC ACID

(a) Procedure of Kipping and Pope[140] - 3-endo-Bromo-D-camphor (14.3 g, 62 mmoles) was sulfonated with 70 ml of 10% fuming sulfuric acid according to the literature procedure and gave 29.36 g

* Addition of sodium borohydride to nickel^{II} salt results in a vigorous exothermic evolution of hydrogen and immediate precipitation of black nickel boride with considerable foaming. The froth can cause ejection of black sludge through the condenser, resulting in the loss of product. Excessive foaming can be subsided by a little methanol. Actual yields are probably better. Jones' oxidation was done to convert any bornanols to camphor-d_2.

of crude sulfonic acid as the sodium salt presumably containing sodium carbonate.

(b) Kauffman's Procedure (Modified)- The literature procedure[66] was modified in as much as a mixture of acetic anhydride (195 ml) and conc. sulfuric acid (61 ml) was used for the sulfonation of 115.5 g (0.5 mole) of 3-endo-bromocamphor. After 6 hrs at 70°, the reaction mixture was cooled and excess of acetic anhydride was distilled off under reduced pressure. The rest of the work up procedure was identical with that of the literature[66] and yielded 184 g (~90%) of the crude ammonium salt of 3-bromocamphor-sulfonic acid.

3-BROMOCAMPHOR-9-SULFONYL CHLORIDE*

The crude sodium salt of 3-bromocamphor-9-sulfonic acid (29.36 g, 116 mmoles) was triturated with 25 g of phosphorus pentachloride at room temperature in a mortar and pestle. The slurry was dissolved in 200 ml of chloroform, washed with cold water, the chloroform solution dried, filtered and the solvent evaporated. The residue came out of petroleum ether as 11.5 g of ill defined crystals, presumably a mixture of epimers at C-3. P.M.R. spectrum: C-3H 4.63 p.p.m. (dd), C-9-CH_2-3.96 p.p.m. (m), Me 1.33 and 1.05 p.p.m. (s.).

3-BROMOCAMPHOR -9-CHLOROSULFOXIDE

Pyridine (40 ml), 38.2 g of p-toluenesulfonyl chloride and 66 g (0.2 mole) of crude 3-bromocamphor-9-sulfonyl chloride were

* Reaction of thionyl chloride with ammonium salt of sulfonic acid is not a neat and repeatable reaction. A tar was formed in one preparation which did not form any chlorosulfoxide. The sodium salt route is recommended.

allowed to react in a manner described for camphor-10-chlorosulfoxide. A reddish powdery mass (44.2 g, 0.142 moles, 71%) was recovered from petroleum ether after work up.
P.M.R. spectrum: C-3HX 4.85 p.p.m. (dd), C-3HN 4.23 p.p.m. (s), Me: 1.23 p.p.m. (6H, s). Epimeric mixture of 3-bromocamphor-9-chlorosulfoxide.

ISOKETOPINIC ACID (Trans)

Crude 3-bromocamphor-9-chlorosulfoxide (20 g, 64 mmoles), 100 ml of water and 100 ml of acetone was magnetically stirred in a 1 l. beaker covered by a watch glass. Sodium carbonate decahydrate (40 g) was added followed by 40 g of potassium permanganate in small portions in 90 min. The reaction was sufficiently exothermic to cause the acetone to boil. After stirring for 1 hour beyond the addition of permanganate, the mixture was filtered through a sintered glass funnel under suction. The filtrate was acidified with concentrated hydrochloric acid and extracted with 4 x 50 ml diethyl ether. The combined ether extracts were worked up to give 12.67 g (75%) of crude 2-oxo-3-bromoapocamphane-9-carboxylic acid as a sticky mass tending to crystallise.
P.M.R. spectrum: carboxyl H 9.38 p.p.m. (1H, exchanges with D_2O), C-3HX 4.8 p.p.m. (dd), C-3HN 4.16 p.p.m. (s), Me 1.25 p.p.m. (6H, s).

Crude 3-bromo-isoketopinic acid (12.2 g, 46.6 mmoles) was dissolved in 30 ml of dioxane and 10 ml of acetic acid in a 250 ml 3-neck round bottom flask fitted with a stirrer, a condenser and a wide bore tygon tubing connected to a sample vial serving as a "hopper". The solution was heated and stirred (reflux

temperatures) and 7 g of zinc dust (B.D.H., Analar) was added in small increments from the "hopper" over 30 min. Stirring with reflux was continued for 4 hrs. After cooling the mixture was filtered, the residue on the funnel washed with 50 ml of diethyl ether, the filtrate diluted with 250 ml of water and extracted with 2 x 50 ml of diethyl ether. The ether extract was worked up to give 7.6 g (91%) of trans isoketopinic acid. Recrystallisation from hot petroleum ether (60-80°) - chloroform gave white crystals, m.p. 248-249.5° (lit.[68] 250° for 2-oxo-D-apobornane - 9-carboxylic acid).

P.M.R. spectrum: acid proton 10.36 p.p.m. (1H, exchanges with D_2O), methyls 1.15 p.p.m. (6H, s). No signals between 3-10 p.p.m.

D-CAMPHOR-9-THIOL-3,9,9-d_3

In a typical preparation 13.4 g (42.7 mmoles) of 3-bromocamphor-9-chlorosulfoxide was treated with 15 g of aluminium amalgam and 15 ml of deuterium oxide in the same way as described for camphor-10-thiol-10-d_2. Work up gave 8.0 g (99%) of oily liquid camphor-9-thiol-3,9,9-d_3 with a faint mercaptan odour which did not crystallise, $[\alpha]_D^{23°}$ + 103° (c = 5.12, ethanol), lit.[141] m.p. 94°, $[\alpha]_D^{22°}$ + 108.7°.

CAMPHOR-9-d_2

Desulfurisation was carried out on 5.0 g (26.7 mmoles) of camphor-9-thiol-3,9,9-d_3 with W4-Raney nickel in refluxing ethanol in the manner described for camphor-10-d_2. After the first treatment (50 g of Raney nickel, 12 hrs) removal of solvent gave 3.2 g of oil with considerable starting material remaining. A second treatment (40 g of Raney nickel, 8 hrs reflux) gave 2.5 g

of wet solid. A passage through neutral alumina gr III in petroleum ether gave 2.1 g of semisolid which was sublimed to yield 1.19 g (28%) of crude camphor-9-d_2, $\nu_{max}^{CS_2}$ 1743 cm^{-1} (C = O), 1380 and 1420 cm^{-1}, $[\alpha]_D^{27°}$ + 43.8° (c = 3.35, ethanol).
P.M.R. spectrum: Me at 0.91 and 0.85 p.p.m. (s), residual C-9-d_2 methyl signal at 0.96 p.p.m. (m).

Mass spec. camphor d_2, 68.5%, camphor d_1, 17.15% and camphor d_0, 14.35%. Major peaks m/e 154, 137, 127, 110, 97, 95, 81 and 69.

CAMPHOR -4-d_1

Ethanol-O-d_1 - Ethyl silicate (110 ml, ~ 102 g, 0.49 mole, Eastman Kodak) was taken in a 250 ml round bottom flask. Deuterium oxide (18 ml, 1 mole, isotopic purity 99.75%) was added followed by a solution of 200 mg of phosphorus pentoxide solution in 0.2 ml of deuterium oxide (i.e. D_3PO_4 catalyst). The contents were refluxed for 2 hrs under a condenser fitted with a Drierite guard tube. Copious amounts of white silica were deposited. The contents were distilled off through a 15-cm Vigreux column into a tared flask. Care was taken in thoroughly drying all the glass units before use. Ethanol-O-d_1 boiling between 78-78.5° was collected. Recovery 72.45 g (1.54 moles, 78.6% on ethyl silicate). Isotopic purity > 99% by P.M.R. spectroscopy.

4-Chloro-isoborneol - D-Camphor (15.23 g, 0.10 mole) was dissolved in 25 ml of methylene chloride in a 2-neck flask fitted with a condenser on an ice bath. Phosphorus trichloride 12.8 g and 22.2 g of phosphorus pentachloride were added through the side neck in small portions. The contents were magnetically stirred. After 2 hrs the temperature was brought to ~ 25° and the reaction mixture

left at this temperature for 10 hrs. The mass was poured on ice and extracted with 200 ml of petroleum ether. The organic layer was washed several times with water till the aqueous phase was essentially free of acid and the 20.8 g of clear colourless liquid residue resulting from the work up was treated with 20 g of potassium acetate, 100 ml 75% ethanol-25% water mixture in a 500 ml round bottom flask and refluxed vigorously on steam bath under a condenser for 12 hrs. After cooling the contents of the flask were poured into 250 ml of water and extracted with petroleum ether (3x, total 200 ml). The petroleum ether solution was worked up as usual to give 16.5 g (96.7 mmoles, 97%) of pale yellow liquid, essentially pure 1-chlorocamphene, optically inactive.

P.M.R. spectrum: Exocyclic methylene 4.91 p.p.m. (d, J = 22.5 c.p.s.), gem dimethyls 1.1 p.p.m. (6H, s).

Crude-1-chlorocamphene (16.2 g, 95 mmoles) was refluxed with 50 ml of formic acid for 14 hrs, the mixture cooled, poured on 200 g of ice, extracted with 200 ml of petroleum ether, and gave 16.76 g (77.3 mmoles, 81%) of deep brown oily crude 4-chloro isobornyl formate after work up.

P.M.R. spectrum: formyl H 8.01 p.p.m. (1H, sharp s), C-2H 4.65 p.p.m. (1H, dd, J2HN, 3HN = 8 c.p.s., J2HN, 3HX = 4 c.p.s.), methyls 1.01, 0.93 and 0.88 p.p.m. (all s).

The crude material (77.3 mmoles) was dissolved in 70 ml of methanol, 5.61 g potassium hydroxide in 30 ml of water was added with cooling and the mixture left for 10 hrs (magnetic stirring) at room temperature. The mixture was then poured on 200 g of ice and extracted with 5x60 ml of diethyl ether. The ether extracts after work up

gave a brownish solid residue which was crystallised from 80 - 100° petroleum ether to give 10.2 g (54 mmoles, 70%) of light yellow crystalline 4-chloro-isoborneol, m.p. 202-203° (sublimes). P.M.R. spectrum: C-2HN at 3.67 p.p.m. (1H, dd, J2HN, 3HN = 7.5 c.p.s., J2HN, 3HX = 4 c.p.s.), hydroxyl proton 1.8 p.p.m. (1H, s), methyls 1.04, 0.97 and 0.85 p.p.m. (s).

4-Chloro-DL-isoborneol (8.0 g, 42.4 mmoles) was dissolved in 45 g of ethanol-O-d_1. Freshly cut sodium (12 g) was added in small cubes through a period of 1 hr while the solution of 4-chloro-isoborneol was vigorously refluxed.* Refluxing was continued for 3 hrs, the mass cooled, 2 ml of deuterium oxide was cautiously added, the mass briefly refluxed again, cooled, diluted with 50 ml of water and extracted with 5 x 20 ml of diethyl ether. The ether extracts were washed with water, dried, filtered and the ether evaporated to leave 6.17 g (40 mmoles, 94%) of crude isoborneol-4-d_1. The crude alcohol was oxidised to ketone without purification.

The whole lot (40 mmoles) was dissolved in 27 ml of acetone in a two neck round bottom flask with a condenser and dropping funnel and was stirred magnetically on an ice bath. Chromium trioxide (3.2 g) dissolved in 15 ml of water and 2.8ml of conc. sulfuric acid was added from the dropping funnel in a period of 15 min. After stirring for 4 hrs, sulfur dioxide was passed in till the solution turned green. The bottom green layer was drawn off, setting aside the top colourless layer, and was extracted with 3 x 25 ml petroleum ether. The ether extract was combined with the

* Essentially the procedure of A. Nickon, et al.[71]

colourless top layer and the mixture extracted with water, saturated sodium bicarbonate solution and saturated brine. The organic layer was dried, filtered and the solvent distilled off. The 6.017 g (39.3 mmoles, 98.7%) of crude DL-camphor-4-d_1 was further purified by sublimation, m.p. 177-179°, single spot in T.L.C. (ethyl acetate-pet. ether 50:50) Rf identical to that of D (+)-camphor on the same plate.

For characterisation 306 mg (2 mmoles) of sublimed material, 800 mg of selenious acid and 0.45 ml of 90% acetic acid were heated in a sealed tube for 4 hrs. After cooling and opening the tube the contents were poured into sodium bicarbonate solution and worked up as described in the milligram scale procedure for preparation of camphor quinone. There was obtained 283 mg (1.69 mmoles, 84%) of crude DL-camphor quinone-4d_1 as a bright yellow solid. Recrystallisation from 80-100° petroleum ether gave 210 mg of bright yellow wooly crystals, m.p. 197-198.5°, lit.[136] 198° for camphor quinone.

P.M.R. spectrum: methyls 0.93 p.p.m. (3H, s) and 1.1 p.p.m. (6H, s). No signal between 2.5-2.83 p.p.m. region (C-4H).

D-CAMPHOR-5-d_1 - 5-exo-Bromo-D-camphor (895.1 mg, 3.87 mmoles) in 20 ml of dry tetrahydrofuran was treated with 1 g of aluminium powder amalgamated with mercuric chloride as described earlier. The suspension was refluxed for one hr while deuterium oxide (1 ml) was added. The residue from the work up was sublimed to yield 436 mg (2.85 mmoles, 73.5%) of camphor-5-d_1.

P.M.R. spectrum showed methyls at 0.95, 0.91 and 0.85 p.p.m. (all s). A signal present in camphor-d_o as a sharp peak at 1.41 p.p.m.

had collapsed to a broad band in camphor-5-d_1.

From the mass spectrum the composition was calculated to be 4% camphor-d_2, 84.6% camphor-d_1 and 11.4% camphor-d_o. Major peaks in the mass spec. were m/e 153, 110, 109, 96, 83, 82, 69, 55 and 41.

The localisation of deuterium atom was confirmed by conversion to 3,3-dibromoderivative. Sublimed camphor-5-d_1 (120 mg, 0.785 mmole) and 320 mg of bromine were heated in a sealed tube at 100° for 1 hr. Work up gave 220 mg (0.71 mmole, 90%) brown oil.

P.M.R. spectrum: C-4H 2.83 p.p.m. (1H, s) broad, $W_{\frac{1}{2}}$ = 6 c.p.s., Me at 1.25, 1.14 and 1.0 p.p.m. (s).

TRICYCLENE[142]- A solution of 10 g (66.7 mmoles) of camphor and 12.3 g (66 mmoles) of p-toluenesulfonyl hydrazine in 50 ml of 1% ethanolic hydrochloric acid was refluxed for 2 hrs. On cooling white acicular crystals deposited which were collected in a filter under suction to give 19.0 g (57 mmoles, 85%) of crude D-camphor-p-toluenesulfonyl hydrazone. Recrystallisation from methanol afforded white needles, m.p. 164.5-165°, lit.[143] 163-164°.

Sodium acetamide reagent was prepared by dissolving 0.4 g of sodium in small pieces in 10 g of molten acetamide, keeping the temperature below 100° under a condenser. After all the sodium was dissolved the melt temperature was held around 80° and 3.8 g (11.9 mmoles) of camphor-p-tosyl hydrazone was added to it. The mixture was slowly heated to 130° and then held at this temperature for 2 hrs. After cooling to ~90° the molten mass was poured in water and extracted with diethyl ether to give 1.109 g (86%) of tricyclene as a white powder after distillation

of ether. A sublimed sample had m.p. 67-67.5° (lit.[144] 67.5-68°), $\nu_{max}^{CS_2}$ 3045 (ΔH), 870, 851, 842 and 815 cm^{-1}. P.M.R. spectrum 1.0 p.p.m. (6H, s) and 0.81 p.p.m. (3H, s).

(This sample contained $<2\%$ camphene and was used for lead tetra acetate oxidation to camphor 2,6-homoenol acetate).

CAMPHOR-6-exo-d_1[#] - In 10 ml methanol-O-d_1, 0.8 g of potassium metal was dissolved and the solution was mixed with a solution of 1.9476 g of the crude oxidation product of tricyclene (containing 60% camphor 2,6-homoenol acetate)* in 5 ml of methanol-O-d_1 and 2 ml of deuterium oxide. After leaving overnight at room temperature the mixture was poured in water, extracted with petroleum ether, and ether extracts evaporated to leave 1.4 g of an oily solid. The entire crude product was chromatographed on 40 g neutral grade III alumina and eluted with petroleum ether to give 901 mg of a white solid from 250 ml forerun. Sublimation gave 750 mg of deuterated camphor as white feathery crystals. P.M.R. spectrum: Me 0.95, 0.91 and 0.85 p.p.m. (all s).

CAMPHOR-6-endo-d_1[+] - In a glass tube 1.92 of crude oxidation product of tricyclene, 6 ml of trifluoroacetic anhydride and 2 ml of deuterium oxide were taken. The tube was sealed and heated at 120° for 6 hrs. After cooling and opening of the tube the dark contents were poured in water, extracted with petroleum ether and

* Sample obtained from W.D. Chambers.
Deuterium was located by bromination of crude deuterio camphors and subsequent reduction to 2-endo-hydroxy-3-endo-bromobornane. The sample from # did not show a long range coupling between 2-exo-proton and a 6-exo-proton, thereby locating deuterium at 6-exo-position. The sample from + showed the presence of the long range coupling and thereby located deuterium at 6-endo-position by exclusion.

the ether extracts were washed with saturated sodium bicarbonate solution and subjected to usual work up to give 825 mg of a brownish oily mass. The entire crude product was chromatographed on 30 g neutral grade III alumina and eluted with petroleum ether-diethyl ether (19:1) to give 462 mg of a light yellow solid from 200 ml forerun, which on sublimation gave 350 mg deuterio camphor as white feathery crystals.

P.M.R. spectrum: Me 0.95, 0.91 and 0.85 p.p.m. (s).

A sample for mass spectral analysis was prepared by digesting 100 mg of the sublimed sample in 10 ml acetic acid and 1 ml perchloric acid in a sealed tube at 150° for 12 hrs. Identical work up as above gave 60 mg of a white solid from petroleum ether extracts. The crude product was resublimed. Mass spec. camphor d_o 24.5%, d_1 74.4% and d_2 1.1%. Major peaks at m/e 153, 110, 108, 95, 83, 82 and 69.

3-HALODERIVATIVES OF LABELLED CAMPHORS

The preparations and work up procedures were essentially those used for preparation of 3-halocamphors from camphor and were scaled down to milligram scale.

3-endo-Bromocamphor-10,10-d_2 - In a glass tube 375 mg (2.43 mmoles) camphor-10,10-d_2 and 0.13 ml (2.43 mmoles) bromine were taken. The tube was sealed and heated at 110° for 8 hrs. After work up the crude product amounted to 400 mg (70%) of an oil, solidifying on cooling. Recrystallisation from methanol gave white crystals, m.p. 74.5-75°.

P.M.R. spectrum (plate 3).

3,3-Dibromocamphor-10,10-d_2 - 3-Bromocamphor-10,10-d_2 (232 mg, 1.0 mmole) was taken in a glass tube cooled in an ice bath. With a micropipette 0.06 ml (1.1 mmoles) bromine was pipetted. After 30 min. the tube was sealed and heated at 100° for 2.5 hrs. Work up gave 302 mg (96%) of a clear pale yellow oil which solidified on cooling. Recrystallisation from petroleum ether gave 135 mg of white needles, m.p. 60-61°.

P.M.R. spectrum: (plate 6), C-10 deuterio methyl at 1.0 p.p.m. (m), collapsed to a singlet on decoupling.

3-endo-Bromocamphor-9-d_1 - In a glass tube 120 mg (0.8 mmole) camphor-9-d_1 and 0.05 ml (0.9 mmole) bromine were taken. The tube was sealed and heated at 100° for 12 hrs. After work up 155 mg (84%) of a solid was obtained which crystallised from methanol in white needles, m.p. 74-75°.

P.M.R. spectrum (plate 3).

3,3-Dibromocamphor-9,9-d_2 - D-Camphor-9,9-d_2 (150 mg, 0.97 mmole) and 0.11 ml (2.1 mmoles) of bromine were taken in a glass tube cooled in ice. The tube was sealed and heated at 100° for 24 hrs. Work up gave 294 mg (95%) yellow oil. The crude product was recrystallised from methanol giving white needles, m.p. 59-59.5°.

P.M.R. spectrum (plate 6), C-9 deuterio methyl (at 1.14 p.p.m. (m), collapsed to a singlet on decoupling.

3-endo-Bromocamphor-4-d_1 - DL-Camphor-4-d_1 (155 mg, 1.0 mmole) and 0.05 ml (0.93 mmole) of bromine were heated in a sealed tube for 2 hrs at 100°. Work up yielded 215 mg (92%) of a pale yellow solid, which crystallised from methanol in white needles, m.p. 74-75°.

P.M.R. spectrum (plate 3).

3,3-Dibromocamphor-4-d_1 - Fisher bromine charcoal reagent, 4.32 g, and 1.551 g (10.0 mmoles) of DL-camphor-4-d_1 were heated in a sealed tube at 110-115° for 4 hrs. Work up gave 2.21 g (71%) of a colourless thick oil which crystallised from methanol in small white needles, m.p. 60-60.5°.

P.M.R. spectrum (plate 6).

3-endo-Chlorocamphor-10,10-d_2 - Camphor-10,10-d_2 (153 mg, 1.0 mmole) and 0.09 ml (1.1 mmoles) of sulfuryl chloride were heated in a sealed tube at 120° for 6 hrs. Work up yielded 172 mg (91.1%) yellowish crystalline solid which crystallised from methanol in white plates, m.p. 95-95.5°.

P.M.R. spectrum (plate 4).

3,3-Dichlorocamphor-10,10-d_2 - Camphor-10,10-d_2 (310 mg, 2.02 mmoles) and 0.32 ml (3.92 mmoles) of sulfuryl chloride were heated in a sealed tube at 120° for 6 hrs. The dark brown contents on work up gave 323 mg of a pale yellow oil, solidifying on cooling. Recrystallisation from methanol was ineffective. The crude product was chromatographed on 10 g neutral grade III alumina. The first eluate (from 50 ml of petroleum ether) gave 220 mg (49%) of a glassy solid which was sublimed, m.p. 93-94°.

P.M.R. spectrum (plate 5).

3-endo-Chlorocamphor-9,9-d_2 - Camphor-9,9-d_2 (302 mg, 1.97 mmoles) and 0.16 ml (1.97 mmoles) of sulfuryl chloride were heated in a sealed tube at 120° for 6 hrs. Work up gave 352 mg (95%) of a semisolid mass which was briefly refluxed in 1 ml of 0.1 N methanolic sodium methoxide and cooled in a dry ice acetone bath to give white flaky crystals, m.p. 94-94.5°.

P.M.R. spectrum (plate 4).

3,3-Dichlorocamphor-9,9-d_2 - 3-endo-Chlorocamphor-9,9-d_2 (115 mg, 0.61 mmole) and 0.06 ml (0.74 mmoles) of sulfuryl chloride were heated in a sealed tube at 120° for 12 hrs to give, after work up, 130 mg of a yellow oil. Sublimation gave 94 mg (52%) of a white solid, m.p. 93-95°.

P.M.R. spectrum (plate 5).

HALOGENATION OF 3-MONOCHALOCAMPHORS

In these experiments ratios of epimeric 3-bromo-3-chlorocamphors were obtained from the P.M.R. spectra of the crude products. Relative area under 2.82 p.p.m. signal corresponded with 3-exo-bromo-3-endo-chlorocamphor and that under 2.68 p.p.m. with 3-endo-bromo-3-exo-chlorocamphor. Crude yields refer to that of epimeric 3-bromo-3-chlorocamphors where these are almost exclusive products of halogenation.

1. BROMINATION OF 3-endo-CHLORO-D-CAMPHOR

a. Lowry's conditions: 3-endo-Chloro-D-camphor (932.4 mg, 5.0 mmoles) and 0.3 ml (5.6 mmoles) bromine were heated on a steam bath under a condenser for 1 hr. The resulting pale yellow fuming liquid was dissolved in petroleum ether and the solvent removed under reduced pressure to give 1.302 g (98%) of a clear transparent oil tending to set into a glassy mass on cooling. P.M.R. spectrum: 2.82 p.p.m. (0.41H), 2.68 p.p.m. (0.59H), 3-monochlorocamphor ~ 2%.

b. In chloroform - acetic acid - A solution of 1.623 g 8.75 mmoles) 3-endo-chlorocamphor in 50 ml of chloroform and 50 ml of acetic acid were mixed with a 10 ml solution of bromine in

acetic acid (1.52 g bromine, 9.5 mmoles) followed by 2 ml of constant boiling hydrobromic acid. The mixture was heated on a water bath ($\sim 100^{\circ}$) for 24 hrs under a condenser, cooled and poured in a solution of 10 g sodium acetate in 50 ml water and extracted with petroleum ether to give 2.268 g (97%) of a glassy solid.

P.M.R. spectrum:2.82 p.p.m. (0.37H), 2.68 p.p.m. (0.63H).

c. In sealed tube - 3-endo-Chlorocamphor (304 mg, 1.64 mmoles) and 0.15 ml (2.8 mmoles) bromine were heated in a sealed tube at $105 \pm 2^{\circ}$ for 1 hr. The contents, after cooling and opening the tube, were poured in a solution of 10 g of sodium acetate in 20 ml of water and extracted with petroleum ether to give 408 mg (93%) of glassy solid.

P.M.R. spectrum 2.82 p.p.m. (0.42H), 2.68 p.p.m. (0.58H).

3-endo-Chlorocamphor (308 mg, 1.65 mmoles), 0.15 ml (2.8 mmoles) of bromine and 0.2 ml of fuming hydrobromic acid were heated in a sealed tube at $104 \pm 2^{\circ}$ for 12 hrs. Work up as before gave 410.1 mg (93%) of 3-bromo-3-chlorocamphors as a glassy solid.

P.M.R. spectrum: 2.82 p.p.m. (0.39H), 2.68 p.p.m. (0.61H).

d. In acetic acid - potassium acetate mixture.

(i) Sealed tube bromination - 3-endo-Chloro-D-camphor (247.5 mg, 1.32 mmoles) in 5 ml of acetic acid and 1 g of potassium acetate were taken in a glass tube. A solution of 310 mg (1.93 mmoles) of bromine in 5 ml acetic acid was added, the tube sealed and heated at 120° for 4 hrs. The bromine colour had entirely vanished and considerable white solid had deposited inside the tube. After cooling and opening the tube the contents were triturated with

water and extracted with petroleum ether to give 2.63 mg of a glassy solid containing 59% monochlorocamphor and 41% 3-bromo-3-chlorocamphors (P.M.R.)

P.M.R. spectrum: 2.82 p.p.m. (0.458H), 2.68 p.p.m. (0.542H), Several repetitions gave identical results (entries 5, 7-9, table VII).

(ii) Control experiment omitting substrate - A mixture of 4 ml of acetic acid containing 600 mg of potassium acetate and a solution of 480 mg (3 mmoles) of bromine in 3,2 ml of acetic acid were heated in a sealed tube at 120° for 4 hrs resulting in complete disappearance of bromine colour and formation of a white precipitate. The tube was cooled and opened, and the white material was collected on a filter under suction and washed several times with methylene chloride to give 654.1 mg (5.5 mmoles) of potassium bromide.

In another experiment 600 mg (10 mmoles) of acetic acid, 115 mg (11.7 mmoles) of potassium acetate and 0.5 ml (9.4 mmoles) of bromine were heated at 100° for 24 hrs. After cooling and opening the tube, the contents were dispersed in dry diethyl ether, filtered, and filtrate evaporated to give 350 mg of a yellow oily liquid.

P.M.R. spectrum: acid proton 10.17 p.p.m. (s), - $\underline{CH_2}O-\overset{O}{\overset{\|}{C}}-$ 3.9 p.p.m. (s), $\underline{CH_3}\overset{O}{\overset{\|}{C}}$ - 2.13 p.p.m. (s). There was a feeble signal at 5.87 p.p.m. (s).

(iii) Control experiment omitting bromine - 3,3-Dibromocamphor (191.8 mg, 0.62 mmoles), 600 mg of potassium acetate and 4 ml of acetic acid were heated in a sealed tube at 120° for 4 hrs, No

white precipitate was detected. The tube was cooled and opened, the contents poured in water and extracted with ether to give 187.8 mg (98%) of 3,3-dibromocamphor as a white crystalline solid identified by P.M.R. spectroscopy.

(e) In 75% acetonitrile - 25% water - 3-endo-Chloro-D-camphor (381.5 mg, 2.04 mmoles), 1 g of potassium acetate and 25 ml of water were taken in a volumetric flask. The volume was made up to 100 ml with acetonitrile after adding 1 g of bromine. The mixture was shaken thoroughly and placed in a thermostat at 25 ± 0.01° for 110 hrs 45 min. The mixture was poured in large volume of water, extracted with petroleum ether, and the extracts washed with sodium bisulfite solution, water, dried, filtered and evaporated to give 347.5 mg white solid containing 70% of 3-chlorocamphors and 30% of epimeric 3-bromo-3-chlorocamphors (P.M.R.).
T.L.C. (Pet. ether, benzene, chloroform: 35:15:2.5) gave 3 spots, Rf 0.33 (~25%), 3-bromo-3-chlorocamphors), 0.19 (~5%) and 0.09 (70%, 3-chlorocamphor). The entire crude product was chromatographed on 40 g neutral grade III alumina. The forerun from 150 ml petroleum ether gave 94.3 mg oil, largely 3-bromo-3-chlorocamphors. Later fractions were 3-chlorocamphor.
P.M.R. spectrum: 2.82 p.p.m. (0.2H) and 2.68 p.p.m. (0.8H), proportion unchanged in the crude and in the chromatographed product.

2. CHLORINATION OF 3-endo-BROMOCAMPHOR

(a) Lowry's conditions - 3-endo-Bromo-D-camphor (462 mg, 2.0 mmoles) and 0.19 ml (2.35 mmoles) of sulfuryl chloride were heated in a sealed tube for 4 hrs at 110 ± 2°. Work up gave 512 mg (96%) 3-bromo-3-chlorocamphor epimers as a glassy solid.

P.M.R. spectrum 2.82 p.p.m. (0.568H), 2.68 p.p.m. (0.432H). A duplicate run gave these ratios as 0.58 and 0.42 respectively (entries 10 and 11 Table VII).

(b) In acetic acid -potassium acetate - 3-endo-Bromo-camphor (~ 1.5 mmoles), potassium acetate (600-1800 mg) and chlorine in acetic acid were heated in sealed tubes for 1 hr at 120°. After cooling and opening the tubes the contents were poured in water and extracted with petroleum ether. The neutral crude product left on evaporation of the solvent was examined by P.M.R. spectroscopy (entries 12-14, Table VII).

A control experiment, omitting the substrate resulted in complete disappearance of chlorine. The aqueous solution of the crude reaction mixture gave 381 mg (2.65 mmoles) of silver chloride from 97.6 mg (1.37 mmoles) of chlorine in a gravimetric estimation.

CHLORINATION OF 3-BROMOCAMPHOR SODIUM ENOLATE

(a) At - 70° - A solution of 4.6 g (19.9 mmoles) of 3-endo-bromo-D-camphor in 20 ml of tetrahydrofuran was added through a dropping funnel during 30 min to a stirred suspension of 855 mg (20 mmoles) of sodium hydride (mineral oil dispersion containing 56.2% active hydride, Metal hydride Inc.) in 50 ml of tetrahydrofuran under a condenser. Absolute ethanol (0.2 ml) was added to start the reaction and the mass refluxed for 2 hrs with continuous stirring. The suspension gradually attained red colour. The flask was cooled to room temperature and then to -70° in a dry ice-acetone bath. The dropping funnel was replaced by a delivery tube and dry chlorine gas bubbled in the mixture for 1 hr. The

mixture was brought to 0°, and 200 mls of a 10% solution of sodium acetate added followed by extraction with petroleum ether giving 4.8 g of an oil containing a mixture of 3-monobromocamphors, 3-bromo-3-chlorocamphors and an impurity with absorption at 4.1-3.3 p.p.m.

P.M.R. spectrum: 2.82 p.p.m. (0.35H) 2.68 p.plm. (0.65H).

A 3.0 g sample of the crude product was chromatographed on 100 g of neutral grade IV alumina to give 177 mg 3-monobromocamphor (from first 100 ml of petroleum ether eluate) and 1.955 g of a solid, largely 3-bromo-3-chlorocamphors with some monobromocamphor (from second 100 ml eluate). The second fraction was rechromatographed and the resulting solid crystallised from methanol to yield an epimeric mixture of 3-bromo-3-chlorocamphors m.p. 50-56°, free of monobromocamphor.

P.M.R. spectrum 2.82 p.p.m. (0.35H) 2.68 p.p.m. (0.65H).

Anal. calc. for $C_{10}H_{14}OBrCl$ (265.5) Br, 30.1; Cl, 13.4.

Found: Br, 29.53; Cl, 13.01.

Repetition of the above experiment gave from 2.3 g (10 mmoles) of 3-endo-bromocamphor, 2.05 g of product, containing 3-monobromocamphor and 3-bromo-3-chlorocamphors.

P.M.R. spectrum 2.82 p.p.m. (0.325H) 2.68 p.p.m. (0.675 H).

(b) At 0° - 3-endo-Bromocamphor (2.30 g, 10.0 mmoles) was treated with sodium hydride as before, the mixture cooled to 0° and chlorine gas passed in it for 1 hr. Work up gave 2.2 g of an oily mass.

P.M.R. spectrum 2.82 p.p.m. (0.443H), 2.68 p.p.m. (0.557H).

HALOGENATION OF 3-HALOCAMPHOR LITHIUM ENOLATES

General - Reactions of 3-halocamphors with lithium alkyls were carried out under nitrogen.

The 'direct' addition assembly consisted of a 3-neck round bottom flask fitted with a mechanically driven stirrer (Ace glass, 24/4oground glass joint, teflon blade), a condenser and a serum vial cap (septum) snugly fitting the side arm. Nitrogen (purified by passage through Fieser's solution, conc. sulfuric acid, phosphorus pentoxide and a glass wool 'trap') entered the reactor flask from a syringe needle inserted in the rubber septum and came out from the top of the condenser which was connected to a mercury well to provide a pressure of 0.2-0.5 cms of Hg. All joints were sealed with a light coating of thick mineral oil. Reagents were injected with a Yale syringe fitted with a no. 20 needle through the septum in the reactor. The reactor flask was surrounded with a polythene container which could be filled with cooling solutions at the desired temperature. Nitrogen was passed 20-30 min before the reaction was started and the system was kept under a nitrogen blanket throughout the reaction period.

The 'reverse' addition assembly had similar arrangement to generate enolates except that the reactor chamber (upper chamber in this case) was connected to another, lower chamber, through a stop cock. Reagents for trapping the enolate were held in the lower chamber and the enolate could be added to the trapping agent (reverse addition).

STANDARDISATION OF ALKYLLITHIUMS

(a) With Bromocamphor - n-Hexane (25 ml) and n-butyllith-

ium (2.5 ml, 1.6M in hexane, Foote Mineral Co.) were taken in the "direct" reactor along with 100 mg of triphenyl methyl chloride. A pale yellow colour developed. Nitrogen was passed and after 20 min a solution of 1.15 g (5.00 mmoles) of 3-endo-bromocamphor in 25 ml of hexane was introduced through a burette with its tip inserted in the reactor through the rubber septum. The mass was stirred. The red colour first appeared which changed into yellow-brown shade with addition of 20.1 ml of solution, giving strength of n-butyl lithium 1.6M.

(b) With Acetone - Triphenylmethyl chloride (125 mg, 0.48 mmole) and 10 ml of n-butyllithium solution were taken in the "direct" reactor under nitrogen. A pale yellow colour appeared. Spectral grade acetone was added through a microburette as before. First few drops caused appearance of a deep ochre colour. Total acetone required for change of ochre shade to permanent yellow shade was 1.04 ml, giving the strength of n-butyllithium 1.4M.

GENERATION OF LITHIUM ENOLATES OF 3-BROMOCAMPHOR

(a) In a typical experiment 1.156 g (5.00 mmoles) of 3-endo-bromocamphor and 44 ml of dry tetrahydrofuran were taken in the "direct" reactor and flushed with nitrogen. The cooling bath was fillted with dry ice-acetone mixture at -70°. After 20 min n-butyllithium (6 mls, 1.6 M in hexane, 9.6 mmoles) was injected cautiously. Internal temperature recorded by a thermometer hanging within the condenser was kept between -70° to -65° during the addition of base. Stirring was continued for 4 hrs. Water (1 ml) was added to protonate the carbon bases, the reaction mixture poured into water and extracted with petroleum ether. The aqueous layer

was concentrated to about half its volume, acidified with 10 ml of 10% nitric acid and halide ions were precipitated by 10 ml of 10% silver nitrate as silver halides and estimated gravimetrically. Dry weight of silver bromide was 676.6 mg (3.6 mmoles, 72%). The petroleum ether layer was washed, dried, filtered and evaporated to give a glassy solid.

P.M.R. spectroscopy indicated a mixture of camphor (70-80%) and 3-bromocamphor (20-30%).

(b) 3-endo-Bromocamphor (1.155 g, 5.00 mmoles) in 44 ml of dry tetrahydrofuran was treated with 6 ml of n-butyllithium (9.6 mmoles) as above. Sulfuryl chloride (1 ml, 12.4 mmoles) was injected and the mixture stirred at -70° for 1 hr. The mixture was brought to 0°, 1 ml of water was added, and the contents of the reactor were poured in a large volume of water and extracted with petroleum ether. The petroleum ether extract was washed with water, dried, filtered and evaporated to give a glassy solid. P.M.R. spectroscopy gave 3-endo-bromocamphor 13.8%, 3-endo-chlorocamphor 19.5% and 3-exo-chlorocamphor 66.7%. Dehalogenation (enolate trapped as monochlorocamphor) was 86.2%.

Identical procedure was used to study the effect of temperature, solvent and base concentration on the preference for proton removal versus halogen metal exchange in 3-endo-bromocamphor and 3-endo-chlorocamphor. Results appear in table XII.

CHLORINATION OF 3-BROMOCAMPHOR LITHIUM ENOLATE

(a) With chlorine - Dry chlorine gas was passed in 200 ml of carbon tetrachloride. A 1 ml aliquot was pipetted into 10 ml of 10% potassium iodide and liberated iodine titrated against 0.1N sodium thiosulfate to starch end point. Strength of chlorine solu-

tion was calculated from thiosulfate consumed.

3-endo-Bromocamphor (4.62 g,20 mmoles) was taken in 172 ml of dry tetrahydrofuran. After flushing with nitrogen (in "direct" reactor) for 30 min, 28 ml of 1.6 M (44.8 mmoles) n-butyllithium was injected at room temperature (inside temperature rose to 50° during the addition of base). After stirring for 2 hrs at room temperature the cooling bath was filled with dry ice-acetone mixture to give inside temperature -70°. Chlorine solution (112 mls, 47 mmoles) was injected. The temperature rose to -65° and the mixture, originally light yellow turned to very pale green. After stirring for 2 hrs, the mixture was allowed to warm up, the contents of the reactor poured in 100 ml water, the aqueous layer separated from the mixture and organic layer washed with 25 ml of 10% sodium bisulfite solution, water, saturated brine, dried, filtered and evaporated to leave 5.78 g of a pale yellow oil. P.M.R. spectrum showed an unidentified impurity with signals between 4.1 to 3.3 p.p.m. The area under 2.82 p.p.m. corresponded to 39.8% of 3-exo-bromo-3-endo-chlorocamphor and under 2.68 p.p.m. corresponded to 60.2% of the 3-endo-bromo-3-exo-chlorocamphor.

Chlorination at room temperature ($\sim$25°) followed similar steps.

(b) With t-butylhypochlorite - A solution of t-butylhypochlorite in carbon tetrachloride was prepared following the directions of Zavitsas.[145]

3-Bromocamphor (4.645 g, 20.0 mmoles) in 172 ml of tetrahydrofuran was reacted with 28 ml of 1.6 M (44.8 mmoles) n-butyllithium solution at room temperature. After 2 hrs the mixture was

cooled to -70° and 45 ml of 0.99 N t-butylhypochlorite solution injected. Stirring was continued at -70° for 2 hrs and 5 ml of acetic acid was injected. The mixture was extracted with petroleum ether to give 5.197 g of an oily liquid.

P.M.R. spectrum 2.82 p.p.m. (0.188H), 2.68 p.p.m. (0.812H).

The crude product was dissolved in 20 ml of methanol and cooled in a dry ice acetone bath. On scratching the sides of the container a white crystalline solid deposited which was collected under suction on a filter, to give after four more crystallisations 2.3 g (43%) of 3-bromo-3-chlorocamphor epimers as a white solid, m.p. 52-62.5°.

P.M.R. spectrum 2.82 p.p.m. (0.225H), 2.68 p.p.m. (0.775H).

Lithium enolates of 3-bromocamphor were also chlorinated with t-butyl hypochlorite at room temperature and at -100° in identical procedure. Results appear in table VIII.

(c) Reverse addition of 3-bromocamphor lithium enolate to chlorine -

In the upper chamber of reverse addition assembly a solution of 1.155 g (5.0 mmoles) of 3-endo-bromocamphor in 50 ml of tetrahydrofuran was taken. n-Butyllithium (4 ml of a 1.6 M solution, 6.4 mmoles) was injected at room temperature. After 10 min the solution of lithium enolate was added dropwise to a solution of 10 ml of 1.25 M (12.5 mmoles) chlorine and 40 ml of petroleum ether stirred magnetically under nitrogen in the lower chamber. Five minutes after the addition was over, the reaction mixture was poured into 250 ml of water and extracted with petroleum ether. The aqueous layer was faintly acidic (pH~4.5). The petroleum extract after washing with saturated sodium bisulfite solution

and work up gave 1.09 g of a light yellow oil.
P.M.R. spectrum 2.82 p.p.m. (0.37H), 2.68 p.p.m. (0.63H). There were unidentified signals between 4.1-3.3 p.p.m.

(d) Chlorination with N-chlorosuccinimide - 3-endo-Bromocamphor (1.16 g, 5.0 mmoles) in 44 ml of tetrahydrofuran was reacted with 6 mls of 1.6M (9.6 mmoles) methyllithium solution in ether at room temperature in the direct reactor. After 2 hrs, 1.67 g (12.5 mmoles) of N-chlorosuccinimide (Aldrich) in 20 ml of tetrahydrofuran was injected at room temperature. A thick white precipitate formed. After 2 hrs, the mass was poured in 100 ml of water, taken up in 100 ml petroleum ether and the ether extract washed, dried and filtered to give 1.32 g oil, containing 3-endo-bromocamphor and 3-bromo-3-chlorocamphors.
P.M.R. spectrum 2.82 p.p.m. (0.38H), 2.68 p.p.m. (0.62H).

(e) Chlorination with DABCO-Chlorine Adduct - Triethylene diamine (DABCO, Aldrich) (4.48 g, 40 mmoles) was dissolved in 50 ml of carbon tetrachloride. Chlorine solution in carbon tetrachloride (30 ml of 0.86 M, 25.8 mmoles) was added while the solution was stirred. A pale yellow solid precipitated immediately, which was filtered and washed with carbon tetrachloride. The filtrate gave negative starch-iodide test. The solid was water soluble and liberated iodine from potassium iodide. During attempted drying the mass turned into a yellow, sticky liquid, insoluble in carbon tetrachloride, soluble in water and did not liberate iodine from potassium iodide. Aqueous solution of this liquid was acidified with dilute sulfuric acid and diluted with ethanol. A portion of the ethanolic solution gave a yellow precipitate with 2,4-dinitrophenyl hydrazine reagent, m.p. 165-165.5° after recrys-

tallisation from methanol (lit.[146] for DNP of formaldehyde 167°). Another portion gave a white adduct with dimedone, m.p. 189-190° (lit.[146] for methone adduct of formaldehyde 189°).

A 2:1 adduct of chlorine-DABCO was prepared by mixing a solution of 2.24 g (20 mmoles) DABCO in 50 ml of carbon tetrachloride and 50 ml of 0.86 M (43.0 mmoles) chlorine in carbon tetrachloride. A sticky white precipitate formed, which was collected on a filter under suction and washed free of excess chlorine by carbon tetrachloride. This adduct was stable (no change in appearance) for 72 hrs under vacuum.

3-Bromocamphor (2.31 g, 10.0 mmoles) was taken in 50 ml of tetrahydrofuran in direct reactor. t-Butyllithium solution in pentane (11.5 ml, 1.35 M, 15.5 mmoles) was injected at room temperature. After 2 hrs, a suspension of the chlorine-DABCO (2:1) adduct in carbon tetrachloride (from 20 mmoles DABCO) was added. Work up gave 3.734 g of a pale yellow oil. The aqueous layer gave a yellow precipitate with 2,4-dinitrophenyl hydrazine reagent. The oily product from petroleum ether solution gave two spots on a silica gel plate (petroleum ether: ethylacetate, 70: 30), the first spot with high Rf did not correspond to 3-bromo-3-chlorocamphors. The mixture was filtered, and the filtrate (methanol solution) on evaporation gave 2.171 g of a solid, identified by P.M.R. spectroscopy to be largely 3-monobromocamphor (with traces of camphor). There was no signal in 2.82-268 p.p.m. region.

(f) Triethylamine - Chlorine Adduct - Triethylamine (2.547 g, 25 mmoles) in 25 ml of carbon tetrachloride and 15 ml of 1.3 M

(19.5 mmoles) chlorine solution in the same solvent were mixed to form a white precipitate. This suspension was added to a solution of 3-bromocamphor lithium enolate generated from 1.163 g (5 mmoles) of 3-endo-bromocamphor in 50 ml of tetrahydrofuran and 7.5 ml of 1.35 M (10.3 mmoles) t-butyllithium. After 24 hrs of stirring 5 ml acetic acid was injected and the mixture worked up as before. Petroleum ether extract on evaporation left 1.152 g of a solid revealed to be monobromocamphor and camphor by P.M.R. spectroscopy.

(g) 2,6-Lutidine - Chlorine Adduct - A solution of 2.72 g (25 mmoles) 2,6-lutidine in 30 ml carbon tetrachloride and 16 ml of 1.3 M (20.8 mmoles) chlorine in the same solvent were mixed. The colour changed to yellow. 3-Bromocamphor lithium enolate from 1.164 g (5 mmoles) 3-endo-bromocamphor and 7.5 ml of 1.35 M (10.0 mmoles) t-butyllithium in 50 ml tetrahydrofuran was generated in the direct reactor. The lutidine-chlorine solution was injected in. After 2 hrs, 10 ml water was injected and the mixture worked up as before to give 1.35 g of a dark brown oil. P.M.R. spectrum 2.82 p.p.m. (0.77H), 2.68 p.p.m. (0.23H).

(h) With Sulfuryl Chloride - 3-Bromocamphor lithium enolate was generated from 1.156 g (5 mmoles) of 3-endo-bromocamphor and 7 ml of 1.6 M (11.2 mmoles) methyllithium in tetrahydrofuran. Freshly distilled sulfuryl chloride (0.8 ml, 1.336 g, 10 mmoles) in 10 ml of carbon tetrachloride was injected at room temperature. Work up gave 1.025 g oil whose P.M.R. spectrum gave signals at 2.82 p.p.m. and 2.68 p.p.m., corresponding to 76.9% and 23.1% respectively.

BROMINATION OF 3-CHLOROCAMPHOR LITHIUM ENOLATES

(a) With bromine - 3-endo-Chlorocamphor (1.86 g, 10.0 mmoles) and 37.5 ml of dry tetrahydrofuran were taken in the direct reactor. A 1.6 M (12.5 ml, 20.0 mmoles) solution of n-butyllithium was injected at room temperature. After 3 hrs a solution of 20 mmoles bromine in 20 ml of carbon tetrachloride was injected and the mixture stirred for 3 hrs. The contents of the reactor were poured into 100 ml of water and worked up to give 1.84 g of an oily liquid containing about equal amounts of 3-chlorocamphor and 3-bromo-3-chlorocamphors and an impurity with signals around 4.1-3.3 p.p.m.

P.M.R. spectrum 2.82 p.p.m. (0.642H), 2.68 p.p.m. (0.358H).

(b) With N-bromosuccinimide - A solution of 1.87 g (10.0 mmoles) 3-endo-chlorocamphor in 38 ml of tetrahydrofuran was taken in the direct reactor. t-Butyllithium (12 ml of 1.35 N, 16.2 mmoles) was injected at room temperature. After 8 hrs a solution of 2.9 g (16.5 mmoles) of N-bromosuccinimide in 40 ml of tetrahydrofuran was injected. The mixture turned into a violet jelly. Stirring was continued for 12 hrs and 10 ml of water was introduced to dissolve the jelly (pale brown at this stage). The mixture was extracted with petroleum ether to give 2.487 g of an oily liquid containing some monochlorocamphor and mainly 3-bromo-3-chlorocamphors.

P.M.R. spectrum 2.82 p.p.m. (0.655H), 2.68 p.p.m. (0.345H).

SELECTIVE DEHALOGENATION OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

(a) By triphenylphosphine - Several experiments were carried out. In a typical experiment 278 mg (1.05 mmoles) of epimeric 3-bromo-3-chlorocamphors (containing 50% of each epimer)

was dissolved in 10 ml of methanol. Triphenylphosphine (255 mg, 0.97 mmoles) was added and the mixture refluxed for 1 hr. After cooling the solution was poured into 50 ml of water and extracted with petroleum ether to give 208 mg of a glassy solid containing 3-endo-chlorocamphor (none of the 3-exo-chlorocamphor), and a small proportion of 3-bromo-3-chlorocamphors identified by P.M.R. spectroscopy. T.L.C. (petroleum ether-benzene, 70:30) gave only two spots corresponding to 3-endo-chlorocamphor (major component) and 3-bromo-3-chlorocamphors (minor component).
P.M.R. spectrum 2.82 p.p.m. (0.113H), 2.68 p.p.m. (0.887H).

Results of dehalogenation at other temperatures appear in table X.

(b) Dehalogenation by iodide ion - A solution containing 348 mg (1.31 mmoles) of 3-bromo-3-chlorocamphors and 1.98 g (13.2 mmoles) of sodium iodide in 13 ml of methyl ethyl ketone was refluxed for 4 hrs. The yellow coloured solution was poured into 50 ml of water and sodium thiosulfate solution was added till the colour of iodine was discharged. The mixture was extracted with petroleum ether to give 325 mg of an acrid smelling oil.
P.M.R. spectrum 2.82 p.p.m. (0.78H), 2.68 p.p.m. (0.22H) in the starting compound; 2.82 p.p.m. (0.75H), 2.68 p.p.m. (0.25H) in the product.

(c) Dehalogenation by thiourea - A solution of 270 mg (1.01 mmoles) 3-bromo-3-chlorocamphors and 76 mg (1 mmole) of thiourea in 2 ml of ethanol was refluxed for 18 hrs. The mixture was poured into 50 ml of water and extracted with petroleum ether to give 245 mg of a solid.

P.M.R. spectrum 2.82 p.p.m. (0.75H), 2.68 p.p.m. (0.25H) in the starting compound; 2.82 p.p.m. (0.73H), 2.68 p.p.m. (0.27 H) in the product.

(d) Dehalogenation by methoxide ion - 3-Bromo-3-chlorocamphors (266 mg, 1.0 mmole) was taken in 5 ml of 0.1 M methanolic sodium methoxide and the mixture heated in a sealed tube at 120° for 6 hrs. After cooling and opening of the tube, the contents were poured into 50 ml of water and extracted with petroleum ether. The aqueous extracts gave 91.5 mg (0.486 mmole if all silver bromide) of silver halide in a gravimetric estimation. The petroleum ether extracts gave 180 mg of a solid containing 9% of monochlorocamphor and 91% 3-bromo-3-chlorocamphors.
P.M.R. spectrum 2.82 p.p.m. (0.276H), 2.68 p.p.m. (0.724H) in the starting material and 2.82 p.p.m. (0.273H), 2.68 p.p.m. (0.727H) in the products.

(e) Dehalogenation by t-butoxide ion - 3-bromo-3-chlorocamphors (266 mg, 1.0 mmoles) and 3 ml of 0.1N sodium t-butoxide in t-butyl alcohol were heated in a sealed tube for 10 hrs at 120°. Work up gave 172 mg of a glassy solid.
P.M.R. spectrum 2.82 p.p.m. (0.40H), 2.68 p.p.m. (0.60H) in the starting material and 2.82 p.p.m. (0.375H), 2.68 p.p.m. (0.625H) in the products.

(f) Dehalogenation with 2,6-lutidine - Ethylene glycol (2 ml), 2,6-lutidine (214 mg, 2.0 mmoles) and 3-bromo-3-chlorocamphors (282 mg, 1.06 mmoles) were heated in a sealed tube at 155° for 4 hrs. Work up yielded 230 mg of a yellow solid, containing 58.5% monochlorocamphor and 41.5% of 3-bromo-3-chlorocamphors.

P.M.R. spectrum 2.82 p.p.m. (0.26H), 2.68 p.p.m. (0.74H) in the starting compound; 2.82 p.p.m. (0.26H), 2.68 p.p.m. (0.74H) in the products.

The aqueous extracts during the work up gave 113 mg of silver halide (0.60 mmole, if silver bromide).

(g) Dehalogenation with alkyllithiums - A solution of 268 mg (1.01 mmoles) of 3-bromo-3-chlorocamphors in 10 ml of n-hexane in the direct reactor under nitrogen was treated with 1 ml of a 1.35 M solution (1.35 mmoles) of n-butyllithium for 15 min. Acetic acid (1 ml) was injected to destroy the bases, and the reaction mixture extracted with petroleum ether to give 170 mg of 3-chlorocamphor as a white solid. Aqueous extracts gave 185 mg of silver halides in a gravimetric estimation (0.985 mmole if all silver bromide).

In a separate run 270 mg (1.01 mmoles) of 3-bromo-3-chlorocamphors in 10 ml of n-hexane were treated with 0.41 ml of 1.35 M solution (0.55 mmole) of t-butyllithium for 2.5 hrs at room temperature. Work up yielded 210 mg of a solid product containing 12.5% of monochlorocamphor, 42.5% of monobromocamphor and 45% of epimeric 3-bromo-3-chlorocamphors.
P.M.R. spectrum 2.82 p.p.m. (0.733H), 2.68 p.p.m. (0.267 p.p.m.) in the starting material and 2.82 p.p.m. (0.572H), 2.68 p.p.m. (0.428) in the product.

(h) Dehalogenation with sodium cyanide - 3-bromo-3-chlorocamphor (207 mg, 0.78 mmole), sodium cyanide (31.3 mg, 0.64 mmole) in 10.5 ml of water and 100 ml of dimethyl formamide were heated at 130° for 12 hrs. The mixture was poured into a large excess of water and extracted with petroleum ether to give 149.3 mg of a

semi solid product containing 70% of monochlorocamphor and 30% of 3-bromo-3-chlorocamphors,
P.M.R. spectrum 2.82 p.p.m. (0.22H), 2.68 p.p.m. (0.78H) in the starting material; 2.82 p.p.m. (0.086H), 2.68 p.p.m. (0.914H) in the product.

The aqueous extracts from the work up gave 110.6 mg of silver halides (0.588 mmole if silver bromide).

(i) Dehalogenation with sodium borohydride - A solution of 661 mg (2.49 mmoles) of 3-bromo-3-chlorocamphors in 12.5 ml of 90% methanol was stirred magnetically. Sodium borohydride (94.5 mg) was added in small portions. After 30 min the solution was poured into 50 ml of water and extracted with petroleum ether to give 480 mg of a glassy solid.
P.M.R. spectrum 2.82 p.p.m. (0.34H), 2.68 p.p.m. (0.66H) in the starting material; 2.82 p.p.m. (0.216H), 2.68 p.p.m. (0.784H) in the product.

(j) Dehalogenation with zinc. - A solution of 267 mg (1.0 mmole) of 3-bromo-3-chlorocamphors in 10 ml of acetic acid was refluxed under a condenser. Zinc powder (B.D.H., Analar, 33 mg, 0.5 mmole) was added while the refluxing solution was stirred magnetically. After 30 min, the mixture was cooled and poured into 50 ml of cold water and extracted with petroleum ether to give 198 mg of a solid containing 47.5% of chlorocamphor and 52.5% of epimeric 3-bromo-3-chlorocamphor.
P.M.R. spectrum 2.82 p.p.m. (0.386H), 2.68 p.p.m. (0.614H) in the starting material; 2.82 p.p.m. (0.384H), 2.68 p.p.m. (0.616H) in the products.

(k) Dehalogenation with tri-n-butyl tin hydride - A solution of 272 mg (1.02 mmoles) of 3-bromo-3-chlorocamphors in 15 ml of dry diethyl ether was taken in the direct reactor under nitrogen. A solution of 150 mg (0.505 mmole) of tri-n-butyl tin hydride in 5 ml of diethyl ether was injected. After 1 hr, the solvent was evaporated under reduced pressure leaving behind 310 mg of a yellow oil containing 3-chlorocamphors, 3-bromo-3-chlorocamphors and an impurity with considerable absorption around 1 p.p.m. (presumably an organotin compound).
P.M.R. spectrum 2.82 p.p.m. (0.38H), 2.68 p.p.m. (0.62H) in the starting material; 2.82 p.p.m. (0.382H), 2.68 p.p.m. (0.618H) in the crude product.

(1) Preparation of 3-endo-bromo-3-exo-chlorocamphor by selective dehalogenation - 3-Bromo-3-chlorocamphors (5.31 g, 20.00 mmoles), and triphenylphosphine (1.572 g, 6.05 mmoles) in 100 ml of methanol solution were stored in a refrigerator for 20 hrs. Work up gave 4.86 g of a glassy solid containing 36% of monohalocamphors and 64% of 3-bromo-3-chlorocamphors. P.M.R. spectrum 2.82 p.p.m. (0.248H), 2.68 p.p.m. (0.752 p.p.m.) in the starting compound; 2.82 p.p.m. (0.116H), 2.68 p.p.m. (0.881H) in the product.

The crude product was chromatographed on 300 g of neutral grade IV alumina giving 2.32 g 3-bromo-3-chlorocamphors free of monohalocamphors (from 100 ml cyclohexane). This product was treated with 342 mg (1.30 mmoles) of triphenylphosphine in 43.5 ml of methanol at refrigerator temperature for 12 hrs giving 1.98 g of a solid product on work up.

P.M.R. spectrum 2.82 p.p.m. (0.097H), 2.68 p.p.m. (0.903H).

Repetition of the above treatment a third time led to a material which after recrystallisation from methanol had m.p. 60-64.5°.

P.M.R. spectrum 2.82 p.p.m.(0.03H), 2.68 p.p.m.(0.97H).

ACETYLATION OF 3-BROMOCAMPHOR LITHIUM ENOLATE

(a) Low temperature enolate formation - 3-endo-Bromocamphor (11.56 g, 50 mmoles) was dissolved in 100 ml of petroleum ether and 50 ml of diethyl ether in the direct reactor. The reactor was cooled in a dry ice acetone bath at -50° and 40 ml of 1.6 N (66 mmoles) solution of n-butyllithium was injected. After 2 hrs the reaction mixture was brought to room temperature and 10 ml (98 mmoles) of acetic anhydride (B.D.H.) was injected. The mixture was continuously stirred under nitrogen, and after 1 hr was poured on ice and extracted with petroleum ether. The ether extracts were washed thrice with saturated potassium bicarbonate solution, dried, filtered and the solvent distilled to give 10.4 g of a yellow oil which was fractionally distilled under reduced pressure. Two fractions were collected, 3.98 g b.p. 90-94°/9 mm and 2.78 g b.p. 102-130°/9 mm.

The 90-94° fraction (3.98 g) was chromatographed on 120 g of neutral grade III alumina. The forerun from 100 ml of petroleum ether gave 2.56 g of a colourless oil which was distilled and a fraction b.p. 92-93°/8.5 mm was collected. This gave a single peak retention time 3.4 min in g.l.p.c. (2-m column of 1% BDS on Chromosorb P at 130°), $[\alpha]_D^{20°}$ + 16.5° (c = 8.16, chloroform), $\nu_{max}^{CS_2}$ 1765 (ester C = 0), 1610 and 1630 (C = C), 1200

cm^{-1} (C-O-C).

P.M.R. spectrum: Vinyl hydrogen 5.54 p.p.m. (d, J = 3.5 c.p.s.), acetate methyl 2.1 p.p.m. (s), other methyls 0.93 p.p.m. (6H, s) and 0.76 p.p.m. (3H, s).

Anal. calculated for $C_{12}H_{18}O_2$ (194.26) C, 74.29; H, 9.34; Found C, 74.28; H, 9.19.

This product was characterised as pure D-camphor enol acetate.

The second fraction, b.p. 102-130°/9 mm contained at least 3 compounds, traces of camphor enol acetate, a C-acylated camphor (d, at 2.61 p.p.m.) and largely 3-bromocamphor enol acetate (acetate Me at 2.15 p.p.m.).

(b) Room temperature enolate formation - 3-endo-Bromocamphor (11.56 g, 50.0 mmoles) in 200 ml of tetrahydrofuran was reacted with 40 ml of 1.65 M (66 mmoles) n-butyllithium at room temperature for 2 hrs. The mixture of enolates was cooled to -50° and 10 ml of acetic anhydride was injected. After stirring for 1 hr at -50° the material was worked up as before to give a pale yellow oil after removal of the solvent. The crude product was distilled under reduced pressure and a fraction (10.29 g) b.p. 90-114°/8.7 mm was collected. This contained 4% bromocamphor, 18.3% of camphor enol acetate and 77.7% of bromocamphor enol acetate. The crude distillate (10.29 g) was chromatographed on 300 g of neutral grade III alumina giving 8.5 g of a colourless oil (eluted by 450 ml of petroleum ether), free of bromocamphor, which was fractionally distilled. The fraction distilling at 114-116°/8.7 mm, 5.95 g (43.6%) was pure 3-bromo-D-camphor enol acetate and gave a single peak in g.l.p.c. $[\alpha]_D^{18°}$ + 37.6° (c = 8.00, chloroform), $\nu_{max}^{CS_2}$ 1770 (acetyl C = O), 1645 cm^{-1} (C = C).

P.M.R. spectrum: C-4 proton 2.41 p.p.m. (d, J = 3 c.p.s.), acetyl methyl 2.15 p.p.m. (s), other methyls 1.03, 0.95 and 0.77 p.p.m. (s).

Anal. calculated for $C_{12}H_{17}O_2Br$ (273.2) C, 52.76; H, 6.27; Br, 29.25. Found C, 53.25, H, 6.48; Br, 29.06.

(c) Large Scale Preparation - 3-endo-Bromocamphor (23.14 g, 0.100 mole) in 250 ml of tetrahydrofuran was reacted with 80 ml of 1.6 M (0.128 mole) n-butyllithium at room temperature for 15 min.

The mixture was cooled to -40° and 20 ml (0.196 mole) of acetic anhydride was injected. The mixture was worked up after 2 hrs to give 25.2 g of a pale yellow oil. Fractional distillation gave 7.8 g (40%) of an oil, b.p. 86-95°/8-9 mm which was almost pure camphor enol acetate (with some camphor) and 14.8 g (54%) of 3-bromocamphor enol acetate, b.p. 113.5-116°/8.5 mm. The pot residue was mainly 3-bromocamphor.

In another preparation 46.2 g of bromocamphor gave 41.6% of pure 3-bromocamphor enol acetate.

ACETYLATION OF 3-CHLOROCAMPHOR LITHIUM ENOLATE

3-endo-Chloro-D-camphor (9.325 g, 50.0 mmoles) in 200 ml of tetrahydrofuran was reacted with 40 ml of 1.65 M (66 mmoles) solution of n-butyllithium at room temperature for 2 hrs. The mixture was cooled to -50°, followed by addition of 10 ml (98 mmoles) of acetic anhydride. After 1 hr stirring at -50° the mixture was worked up as described for the bromocamphor reactions to give a light yellow oil, completely free of camphor enol acetate. The crude product was distilled to give 9.231 g (80.6%)

of almost pure 3-chlorocamphor enol acetate as a colourless oil, b.p. 108-110°/8.8 mm. An analytical sample was prepared by chromatography over neutral grade IV alumina and elution with petroleum ether followed by redistillation, b.p. 102-102.5°/6.8 mm., $[\alpha]_D^{18°}$ + 41.6° (c 10.4, chloroform), $\nu_{max}^{CS_2}$ 1770 (C = O), 1652 (C = C), 1210 and 1188 cm^{-1} (C-O-C).

P.M.R. spectrum: C-4 proton 2.35 p.p.m. (d, J = 3 c.p.s.), acetyl methyl 2.16 p.p.m. (3H, s), other methyls 1.04, 0.93 and 0.77 p.p.m. (s).

Anal. calculated for $C_{12}H_{17}O_2Cl$ (228.71) C, 63.01; H, 7.49; Cl, 15.50. Found C, 63.16; H, 7.22; Cl, 15.84.

ENOL ACYLATION OF CAMPHOR

(a) Attempted enol benzoylation - D-camphor (5.0 g, 32.8 mmoles) and benzoyl chloride (5.0 g, 34.4 mmoles) were refluxed vigorously under a condenser provided with a calcium chloride guard tube. Aliquots were drawn at 12 hrs and 33 hrs and examined by P.M.R. spectroscopy. There was no trace of a vinylic proton between the 5.0-5.8 p.p.m. region. The 33 hr aliquot showed a signal at 6.48 p.p.m. (d, J = 10 c.p.s.), total intensity $\sim$ 1%.

(b) Attempted enol acetylation - D-camphor (5.00 g, 32.8 mmoles) and acetyl chloride (5.0 g, 63.6 mmoles) were refluxed vigorously as before. P.M.R. spectra of aliquots drawn at 12 hr and 24 hr did not show the presence of any vinylic protons in the 5.0-6.0 p.p.m. region.

CAMPHOR LITHIUM ENOLATE

(a) ACETYLATION (CAMPHOR ENOL ACETATE)

A solution of 7.7 g (50.0 mmoles) of D-camphor in 200 ml of

dry tetrahydrofuran was treated with 40 ml of 1.6N (64 mmoles) solution of n-butyllithium in a direct reactor under nitrogen. After 2 hrs the reaction mixture was cooled to -55° and 10 ml (98 mmoles) of acetic anhydride was injected. After stirring for 1 hr at -50° the mixture was brought to room temperature and worked up as in the case of the bromocamphor enol acetate to yield 8.906 g of a neutral, pale yellow oil, containing camphor and camphor enol acetate. The crude product was distilled and 7.88 g of a fraction, b.p. 92-94°/8.6 mm was collected. P.M.R. spectrum of the distillate revealed it to contain 90% camphor enol acetate and 10% camphor.

The above preparation was repeated. From 7.6 g D-camphor was obtained 8.85 g of a crude neutral product. G.l.p.c. analysis of the crude on 1% DEGS on Chromosorb P, at 105° gave two peaks, camphor enol acetate, retention time 4.8 min, and camphor, retention time 3.25 min; relative area 80:20. Distillation alone was not sufficient to get rid of camphor. Purification was effected by chromatography of the distillate on neutral grade III or IV alumina and elution with petroleum ether.

(b) REACTION WITH ETHYL CHLOROFORMATE

D-Camphor (7.62 g, 50.00 mmoles) was taken in a solution of 200 ml of tetrahydrofuran in the direct reactor and reacted with 40 ml of 1.6 M (64 mmoles) solution of n-butyllithium at room temperature. After 30 min the reaction mixture was cooled to -50° and 7.5 ml (70.0 mmoles) of ethyl chloroformate was injected. After 1 hr the mixture was brought to room temperature and worked up as in the case of camphor enol acetate to give a pale yellow

liquid product which was fractionally distilled. A uniform fraction, 8.1 g (72.5%) of a colourless liquid, b.p. 119-120°/9 mm was collected and identified as camphor enol ethyl carbonate, $\nu_{max}^{CS_2}$ 1760 (C = O), 1620 (C = C), 1240 and 1200 cm^{-1} (C-O-C).

P.M.R. spectrum: Vinyl hydrogen 5.53 p.p.m. (1H, d, J = 3.5 c.p.s.), -OC$\underline{H}_2$ 4.25 p.p.m. (2H, m), C-4 hydrogen 2.38 p.p.m. (1H, m), Me of ethyl group 1.33 p.p.m. (3H, t), other methyls 0.96, 0.93 and 0.75 p.p.m. (s).

(c) REACTION WITH METHYLIODIDE

D-Camphor (7.62 g, 50.0 mmoles) in 200 ml dry tetrahydrofuran was reacted with 40 ml of 1.6 M (64 mmoles) solution of n-butyllithium at room temperature. After cooling to -50°, methyl iodide (14.2 g, 100.0 mmoles) was injected. The mixture was stirred for 4 hrs at -50°, gradually brought to room temperature and stirring continued under nitrogen. The progress of the reaction was followed by estimating alkali on aliquots drawn periodically. After 100 hrs stirring at room temperature, the reaction mixture was poured in water and extracted with petroleum ether. Removal of the solvent gave 8.05 g oily liquid which was dissolved in 20 ml of ethanol and cooled in a dry ice acetone bath at -70°. A white crystalline solid separated out. This was collected under suction and recrystallised from methanol to give 6.5 g (78%) of 3-endo-methylcamphor as flaky white crystals, m.p. 37-38° (lit.[147] 38° for 3-methylcamphor).

P.M.R. spectrum: 2.46 p.p.m. (1H, m), 2.01 p.p.m. (1H, m), Me 1.06 p.p.m. (3H, d, J = 6 c.p.s.), 1.01 p.p.m. (3H, s) and 0.9 p.p.m. (6H, s).

D-CAMPHOR ENOL ACETATE - REACTIONS

(a) Stability in acetic anhydride - acetate - acetic acid

Camphor enol acetate (194 mg, 1.00 mmole), acetic acid (60 mg, 1.0 mmole), sodium acetate (164 mg, 2.00 mmoles) and acetic anhydride (2 ml, 19 mmoles) were heated in a sealed tube at 150° for 4 hrs. The tube was cooled and opened; its contents were dispersed in petroleum ether, the dispersion filtered and the filtrate evaporated to leave 117 mg of a wet solid containing largely camphor and traces of acetic anhydride identified by P.M.R. spectroscopy. There was no trace of camphor enol acetate detected.

(b) Stability in acetone - Camphor enol acetate (394 mg, 2.03 mmoles), acetone (0.15 ml, 2.00 mmoles, Fisher spectral grade) and p-toluenesulfonic acid (20 mg, 0.1 mmole) were heated in a sealed tube at 120° for 10 hrs. The tube was cooled, opened and the dark coloured contents were triturated in 50 ml of n-hexane and filtered. The filtrate was evaporated to give 232 mg (76.5%) of crude camphor as a white semi solid, identified by P.M.R. spectroscopy. No other product was detected.

(c) Reaction with hydrogen halides - Camphor enol acetate (120 mg, 0.61 mmole) was taken in a P.M.R. tube, 0.3 ml of acetyl chloride and a drop of T.M.S. were added and the P.M.R. spectrum of the solution run. There was a signal from vinylic hydrogen at 5.55 p.p.m. (d, J = 3 c.p.s.), enol acetate methyl at 2.11 p.p.m. and an acetyl chloride methyl at 2.66 p.p.m. Dry hydrogen chloride was bubbled into the solution through a glass capillary for 3.25 min. Scanning the P.M.R. spectrum with the same settings as before showed complete absence of any signals between

5.0-6.0 p.p.m. and no signal at 2.11 p.p.m. The only methyl signals identified were from camphor and from acetyl chloride.

A reference spectrum of 100 mg of acetyl chloride in 0.3 ml of carbon tetrachloride showed a methyl singlet at 2.63 p.p.m. In a P.M.R. tube a solution of 120 mg (0.61 mmole) camphor enol acetate and 0.3 ml of carbon tetrachloride was prepared. Hydrogen chloride gas was passed in this solution as before. P.M.R. spectrum of this solution after 5 min showed a small quantity of the starting material, the rest being acetyl chloride and camphor.

(d) Reaction with chlorine - Camphor enol acetate (199.4 mg, 1.02 mmoles) was dissolved in 5 ml of acetonitrile, 2.5 ml of a 2N chlorine solution in carbon tetrachloride was added and the mass stirred magnetically for 4 hrs at room temperature. The mixture was taken up in 50 ml of petroleum ether and extracted with water, 10% solution of sodium bisulfite, dried, filtered and evaporated to give 190 mg (99.5%) of 3-chlorocamphors as a solid containing 55% of 3-endo-chlorocamphor and 45% of 3-exo-chlorocamphor estimated by P.M.R. spectroscopy.

(e) Reaction with bromine - Camphor enol acetate (202 mg, 1.04 mmoles) was dissolved in 5 ml of acetonitrile. Bromine (10 ml, 0.102 M, 1.02 mmoles) solution in carbon tetrachloride was added and the mixture shaken for 5 min and diluted with 50 ml of petroleum ether. The solution was washed with water, a 0.1N solution of sodium bisulfite, dried, filtered and evaporated to give 228 mg (95%) of 3-bromocamphor as a pale whitish solid containing 3-endo-bromocamphor 64% and 3-exo-bromoepimer 36%.

(f) Reaction with iodine - Camphor enolacetate (198.1 mg, 1.02

mmoles) in 5 ml of acetonitrile and 3 ml of iodine solution (258.3 mg, 1.01 mmoles) in acetonitrile were stirred for 4 hrs at room temperature. Excess iodine was destroyed by 0.05 N sodium thiosulfate solution and the mixture extracted with diethyl ether to give 210 mg of a viscous liquid containing 40% of camphor and 60% of iodocamphor estimated by P.M.R. spectroscopy.

(g) Reaction with mercuric acetate - Camphor enol acetate (1.9432 g, 10.00 mmoles) was dissolved in 25 ml of methanol. A solution of 4 g of mercuric acetate (Fisher) was prepared in 50 ml of methanol. The two solutions were mixed and stirred magnetically for 2 hrs at room temperature. The solvent was evaporated under reduced pressure till the product was free of acetic anhydride odour. The crude mixture was dissolved in 100 ml of boiling methanol and 25 ml of a saturated solution of sodium chloride was added. A white flocculent precipitate formed and was collected in a filter under suction, after cooling. The resulting white cake on the filter was dispersed in 50 ml of warm water, filtered again under suction and the solid on the filter was washed several times with warm water till the washings were free of mercuric ions. The recovered solid was dispersed in a solution of 200 ml of methanol and 20 ml of water, boiled, cooled and filtered under suction to give 2.97 g (73%) of a mixture of epimeric 3-acetoxymercury camphors, m.p. $> 240^{\circ}$ (starts decomposing above 240°).
P.M.R. spectrum: acetoxy methyl 3.35 p.p.m. (s), C-3-exo-methine hydrogen 3.2 p.p.m. (d, J = 6 c.p.s.), C-3-endo-methine hydrogen 2.63 p.p.m. (s), C-4 hydrogen 2.51 p.p.m. (m), methyls at 1.03, 0.91, 0.9, 0.85, 0.80 and 0.78 p.p.m. (s). (In dimethyl sulfoxide-d_6).

(h) Reaction with potassium permanganate - Camphor enol acetate (1.963 g, 10.0 mmoles) in 50 ml of acetone and 50 ml of an aqueous solution containing 2.4 g (15.4 mmoles) of potassium permanganate and 1 g of sodium bicarbonate were mixed together and the mixture stirred magnetically under a condenser for 12 hrs at room temperature. The mixture was filtered under suction, the residue on the filter washed with 50 ml of acetone, the combined filtrate diluted with water and extracted with diethyl ether to give 1.593 g (95%) of D-camphor quinone as a yellow solid, recrystallised from petroleum ether (60-80°) in long fibrous yellow needles, m.p. 198-199° (lit.[136] 198°).

REACTIONS OF 3-BROMOCAMPHOR ENOL ACETATE

(a) With potassium hydroxide - 3-Bromocamphor enol acetate (260 mg, 0.949 mmole) was refluxed with 20 ml of 5% methanolic potassium hydroxide for 15 min. The mixture was poured on ice and extracted with petroleum ether to give 218.6 mg (99%) of 3-bromocamphor as a white crystalline solid, identified by P.M.R. spectroscopy.

(b) With hydrogen halides - 3-Bromocamphor enol acetate (120 mg, 0.45 mmole) in 0.3 ml of carbon tetrachloride in a P.M.R. tube was treated with anhydrous hydrogen chloride gas for 10 min. A spectrum run after 30 min showed starting material unchanged.

3-Bromocamphor enol acetate (280 mg, 1.02 mmoles) was dissolved in 5 ml of acetic acid to which 1 ml of 48% aqueous hydrobromic acid was added. The mixture was kept at room temperature and after 10 hrs poured into water and extracted with petroleum ether to give 266 mg of a semi solid containing some starting mat-

erial and mainly 3-endo-bromocamphor identified by P.M.R. spectroscopy. Less than 2% of 3-exo-bromocamphor was present if at all. The crude product was treated with a solution of 0.2 ml of 0.5 N potassium hydroxide in 5 ml of methanol under reflux for 5 min, poured in water and extracted with petroleum ether to give 225 mg (95%) of 3-bromocamphor as a crystalline solid containing 90% of 3-endo-epimer and 10% of 3-exo-epimer.

(c) With dehalogenating agents - Aluminium (2 g) was amalgamated with 50 mg of mercuric chloride and suspended in 50 ml of tetrahydrofuran. A solution of 617.9 mg (2.26 mmoles) of 3-bromocamphor enol acetate in 25 ml of tetrahydrofuran and 2 ml of water was added and the mixture stirred for 2 hr at room temperature. The mixture was filtered and the filtrate evaporated to give 505 mg of an oil. The P.M.R. spectrum of the product was devoid of any signals at 5.55 p.p.m. and was the starting material (85%) recovered unchanged.

A solution of 630.5 mg (2.30 mmoles) of 3-bromocamphor enol acetate in 50 ml of diethyl ether was treated under nitrogen with 3 ml of 1M (3 mmoles) tri-n-butyl tin hydride solution in ether for 2 hrs at room temperature with stirring. The solvent was evaporated and the remaining 1.71 g of yellow oil was distilled to give 456.3 mg of an oil, b.p. 108-120°/10 mm. P.M.R. spectroscopy of the distillate revealed it to contain only traces of 3-monobromocamphor, the rest being the starting material unchanged.

(d) Chlorination

(i) In carbon tetrachloride with lithium bromide catalyst

In a mixture of 25 ml of carbon tetrachloride, 25 ml of acetic acid, 50 mg of lithium bromide and 514.6 mg (1.88 mmoles)

of 3-bromocamphor enol acetate was added a 25 ml, 0.75 M solution of chlorine (1.87 mmoles) in carbon tetrachloride. The mixture was stirred at room temperature for 12 hrs, poured on ice, washed successively with water and a 0.1N solution of sodium bisulfite, dried, filtered and evaporated to give 546.3 mg of a solid containing a trace of the starting material and the rest 3-bromo-3-chlorocamphors. Recrystallisation from methanol afforded a white crystalline material, m.p. 58.5-59.5°. P.M.R. spectrum revealed it to be pure epimeric 3-bromo-3-chlorocamphors: 2.82 p.p.m. (0.94H) and 2.68 p.p.m. (0.06H).

A solution of 25 ml of carbon tetrachloride, 25 ml of acetic acid, 30 mg of mercuric oxide, 200 mg of lithium chloride, and 5.569 g (20.4 mmoles) of 3-bromocamphor enol acetate was mixed with 50 ml of 1.45 M (72.5 mmoles) solution of chlorine in carbon tetrachloride and stirred at room temperature for 24 hrs. Work up gave 5.223 g of an oil tending to crystallise on standing and contained 7.3% of 3-monobromocamphor and 92.7% of epimeric 3-bromo-3-chlorocamphors. P.M.R. spectrum of the crude product had C-4 proton signals at 2.82 p.p.m. (0.93H) and 2.68 p.p.m. (0.07H). Recrystallisation from methanol gave 3.7 g (70%) of 3-bromo-3-chlorocamphors free of other impurities, the ratio of C-4 proton signals from the two epimers being same as in the crude product.

(ii) <u>In carbon tetrachloride with iodine catalyst. (Preparation of pure 3-exo-bromo-3-endo-chloro-D-camphor)</u> -

3-Bromo-D-camphor enol acetate (20.0 g, 73.2 mmoles) was dissolved in 50 ml of carbon tetrachloride. A solution of 150 ml

of 0.525 M (78.75 mmoles) chlorine in carbon tetrachloride, and 50 mg of iodine were added and the mixture stirred at room temperature. The progress of the reaction was followed by P.M.R. spectroscopy. In 3 hrs the acetoxymethyl signal at 2.11 p.p.m. was completely replaced by the methyl signal from acetyl chloride at 2.63 p.p.m. The only products identified were acetyl chloride and 3-exo-bromo-3-endo-chlorocamphor. The solvent and acetyl chloride were removed under reduced pressure to give 19.46 g of a pink oil. Two crystallisations from methanol and one from petroleum ether gave 13.56 g (69.5%) of white shining crystals of 100% epimerically pure 3-exo-bromo-3-endo-chloro-D-camphor, m.p. 64-64.5°, $[\alpha]_D^{19°}$ -4.6° (c = 8.03, chloroform), $\nu_{max}^{CS_2}$ 1768 cm.$^{-1}$ (C = O). P.M.R. spectrum: C-4 proton 2.82 p.p.m. (1H, m), no signal at 2.68 p.p.m., methyls 1.25, 1.11 and 1.0 p.p.m. (s).

Anal. calculated for $C_{10}H_{14}OBrCl$ (265.5) C, 45.2; H, 5.32; Cl, 13.37 and Br, 30.1. Found C, 45.16; H, 5.44; Cl, 13.38; Br, 30.16.

(iii) In acetonitrile - These chlorinations were done at -45°, 24.5° and 70°. In a common procedure a solution of ~273 mg (1.0 mmole) of 3-bromocamphor enol acetate in 5 ml acetonitrile was stirred at the desired temperature. Lithium chloride (50 mg) was added, followed by 5 mmole of chlorine solution. After 4 hrs the mixture was taken up in 50 ml of petroleum ether and washed with water and sodium bisulfite solution (0.1N). The petroleum ether solution was dried, filtered and evaporated. The resulting product was examined by P.M.R. spectroscopy. Ratio of the two epimeric chlorobromocamphors in the crude product are given in Table IX (entries 3-5).

(iv) With sulfuryl chloride - A solution of 2.73 g (10.0 mmoles) of 3-bromocamphor enol acetate and 2 g (15 mmoles) of sulfuryl chloride in 50 ml of carbon tetrachloride was refluxed for 4 hrs. The solvent and unreacted sulfuryl chloride were removed under reduced pressure to give 2.72 g of the unchanged starting material.

3-Bromocamphor enol acetate (1.37 g, 5.0 mmoles) and 1 g (7.5 mmoles) of sulfuryl chloride along with 50 mg of lithium chloride were heated under reflux for 3 hrs. P.M.R. spectrum of the reaction mixture contained traces of 3-monobromocamphor, acetyl chloride and epimeric 3-bromo-3-chlorocamphors. Acetyl chloride was removed under reduced pressure and the crude product was crystallised from methanol to give 790 mg (60%) of 3-bromo-3-chlorocamphors free of other impurities.

P.M.R. spectrum 2.82 p.p.m. (0.80H), 2.68 p.p.m. (0.20H).

(v) With N-Chlorosuccinimide - 3-Bromocamphor enol acetate (273 mg, 1.00 mmole), 667 mg (5 mmoles) of N-chlorosuccinimide, 10 ml of 50% aqueous dioxane and 1 ml of acetic acid were heated on a steam bath (98-100°) for 10 hrs. The mixture was poured into 50 ml of petroleum ether and worked up as before to give 265 mg of a semisolid containing traces of dioxane and mostly 3-bromo-3-chlorocamphors.

P.M.R. spectrum: 2.82 p.p.m. (0.80H), 2.68 p.p.m. (0.20H).

BROMINATION OF 3-CHLOROCAMPHOR ENOL ACETATE

(a) In polar medium - 3-Chlorocamphor enol acetate (4.57 g, 20.0 mmoles), 25 ml of carbon tetrachloride and 25 ml of acetic acid were stirred magnetically. A solution of 5 ml of bromine (31.2 mmoles) in 25 ml of acetic acid followed by 50 mg of mercuric

oxide and 200 mg of lithium chloride was added. After 10 hrs at room temperature, the mixture was poured on ice and treated with a saturated solution of sodium bisulfite to destroy excess bromine, followed by extraction with petroleum ether. The petroleum ether extracts after work up gave 5.233 g of an oil containing 2.7% of 3-chlorocamphor and 97.3% of epimeric 3-bromo-3-chlorocamphors. P.M.R. spectrum of the crude product gave signals at 2.82 p.p.m. (0.064H) and 2.68 p.p.m. (0.936H).

The crude product was crystallised twice from methanol to give 3.8 g (71.5%) of pure epimeric 3-bromo-3-chlorocamphors, the epimer ratio being identical to that in the crude product.

(b) In carbon tetrachloride catalysed by iodine.

Preparation of 3-endo-bromo-3-exo-chloro-D-camphor

3-Chloro-D-camphor enol acetate (15.0 g, 65.6 mmoles) and 50 mg of iodine in 50 ml of carbon tetrachloride were stirred at room temperature while 150 ml of a 0.5M (75 mmoles) solutionof bromine in carbon tetrachloride was added. The progress of the reaction was followed by P.M.R. spectroscopy. At 3 hrs the acetoxymethyl signal had vanished. The mixture contained acetyl bromide and 3-bromo-3-chlorocamphors. After pouring on ice, the mixture was treated with a saturated solution of sodium bisulfite till the excess of bromine was destroyed, the organic phase was washed with water, dried, filtered and the solvent evaporated to give 14.2 g of a clear thick liquid which crystallised on cooling.

The P.M.R. spectrum of the crude product revealed it to be epimeric 3-bromo-3-chlorocamphors, containing 3-exo-bromo-3-endo-

chlorocamphor to the extent of 4 ± 1% of the mixture. The crude material was crystallised twice from methanol and once from petroleum ether to yield 11.4 g (65.5%) of white shining crystals of 3-bromo-3-chlorocamphor, m.p. 49-49.5°, $[\alpha]_D^{19}$ + 93° (c = 8.22, chloroform).

A 2.58 g (9.7 mmoles) sample was dissolved in 50 ml of acetonitrile, containing 1 g of potassium acetate and 30 ml of water. This solution was mixed with a solution of 1.31 g (5.00 mmoles) of triphenylphosphine in 50 ml of acetonitrile at room temperature. After 12 hrs the mixture was poured into 500 ml of water and extracted with petroleum ether to give 2.12 g of a crude product after work up. The entire crude product was chromatographed on 60 g of neutral grade I alumina. One litre of petroleum ether eluted 1.51 g of an oil which crystallised on cooling. Two recrystallisations from petroleum ether gave 550 mg (21.3%)of 3-endo-bromo-3-exo-chloro-D-camphor, of 95.45% epimeric purity as large white prisms, m.p. 50-50.5°, $[\alpha]_D^{19°}$ + 96.2° (c = 8.01, chloroform), $\nu_{max}^{CS_2}$ 1768 cm^{-1} (C = 0). P.M.R. spectrum: C-4 proton 2.68 p.p.m. (1H, m), methyls 1.13 p.p.m. (6H, s) and 1.03 p.p.m. (3H, s).

Anal. calculated for $C_{10}H_{14}OBrCl$ (265.5) C, 45.2; H, 5.32; Cl, 13.37; Br, 30.1. Found C, 45.08; H, 5.30; Cl, 13.34; Br, 30.06.

ATTEMPTED EPIMERISATION OF EPIMERIC 3-BROMO-3-CHLOROCAMPHORS

A. With Hydrogen Bromide

1. In carbon tetrachloride - A solution of 269 mg (1.01 mmoles) pure 3-exo-bromo-3-endo-chloro-D-camphor in 0.3 ml of carbon

tetrachloride was taken in a P.M.R. tube. Spectrum was recorded. Dry hydrogen bromide gas was bubbled in the solution through a capillary for 10 min. The tube was sealed and the C-4H region (2.68 to 2.83 p.p.m.) was scanned periodically in a Varian A-60 instrument. No sign of the appearance of 2.68 p.p.m. signal (from 3-endo-bromo-3-exo-chlorocamphor) was detected during 48 hrs.

2. In acetic acid-chloroform: A solution of 265.5 mg (1 mmole) 3-exo-bromo-3-endo-chloro-D-camphor was prepared in 0.25 ml of acetic acid and 0.15 ml chloroform-d_1 in a P.M.R. tube. Spectrum of the starting material was recorded. Hydrogen bromide was passed in the tube for 10 min, the tube sealed and P.M.R. spectrum scanned periodically. No change was detected in the first 24 hrs. The methyl region was altered slightly after 48 hrs. Considerable 3-monochlorocamphor was identified after 96 hrs but there was no sign of any signal at 2.68 p.p.m.

3. In acetic acid: A solution of 267 mg (1.0 mmoles) 3-exo-bromo-3-endo-chlorocamphor in 0.2 ml of acetic acid and 0.1 ml of fuming hydrobromic acid was taken in a P.M.R. tube which was sealed and heated at 100° for 4 hrs. No sign of either debromination or epimerisation was detected.

4. In trifluoroacetic acid: A solution of 261.5 mg (0.985 mmoles) 3-exo-bromo-3-endo-chloro-D-camphor in 5 ml of trifluoroacetic acid was taken in a glass tube held in an ice bath and saturated with dry hydrogen bromide. The tube was sealed and heated at 100° for 50 hrs (light brown colour). After cooling and opening the tube, the contents were poured in 50 ml water, extracted with petroleum ether and the ether solution washed with saturated bicarbonate, water, dried, filtered and solvent evaporated

leaving 235.5 mg of an oil which solidified on cooling.

P.M.R. spectrum of the product revealed it to be a mixture containing 14.7% 3-chlorocamphor and 85.3% 3-exo-bromo-3-endo-chlorocamphor. No signal was detected at 2.68 p.p.m.

A solution of 236 mg (0.89 mmoles) 3-endo-bromo-3-exo-chloro-D-camphor (95 ± 1% pure from the ratio of 2.83 and 2.68 p.p.m. signals) in 5 ml of trifluoroacetic acid in a glass tube was saturated with hydrogen bromide at 0°. The tube was sealed and heated at 100° for 100 hrs. The contents had turned pale brown in colour. After cooling and opening the tube the reaction mixture was processed as before to give 208 mg of a light brown oil which solidified on cooling.

P.M.R. spectrum showed the product to contain 8% monochlorocamphor and 92% epimeric 3-bromo-3-chlorocamphors. The composition of the epimeric 3-bromo-3-chlorocamphors, from the integration of 2.83 p.p.m. and 2.68 p.p.m. signals was identical, within ± 1%, to that of the starting material (no evidence for epimerisation).

5. Control check with 3,3-dibromocamphor: 3,3-Dibromocamphor 314.9 mg (1.01 mmoles) was taken in 5 ml acetic acid in a glass tube. Dry hydrogen bromide was bubbled in the solution for 10 min, the tube was sealed and heated at 100° for 12 hrs. The tube was cooled, opened, contents poured in 50 ml water and extracted with petroleum ether to give 203.2 mg (0.88 mmoles) of 3-monobromocamphor as a white crystalline solid. T.L.C. on silica gel (60-80° petroleum ether, benzene, chloroform, 350:150:25) gave a single spot, Rf identical to that of 3-endo-bromocamphor.

P.M.R. spectrum revealed a mixture of epimeric 3-bromocamphors. No trace of 3,3-dibrocamphor was detected.

B. WITH TRIPHENYL PHOSPHINE

1. In benzene: 3-exo-Bromo-3-endo-chloro-D-camphor (266 mg, 1.0 mmole) was dissolved in 0.2 ml benzene in a P.M.R. tube. A 0.15 ml solution of 262 mg (1 mmole) triphenylphosphine in benzene was pipetted in, the tube sealed and P.M.R. spectrum recorded. A periodic scan was taken of the C-4 proton region. No change was detected after 24 hrs. The tube was then heated at 100° for 50 hrs. Considerable solid deposited leaving a clear yellow supernatant liquid showing in its P.M.R. spectrum complete absence of the starting material.

2. In carbon disulfide: A solution of 266 mg 3-exo-bromo-3-endo-chlorocamphor in 0.2 ml of carbon disulfide and 261 mg of triphenylphosphine in 0.3 ml of carbon disulfide were pipetted in a P.M.R. tube. No sign of epimerisation was observed in the course of 24 hrs.

3. In acetonitrile: A solution of 132.7 mg 3-exo-bromo-3-endo-chlorocamphor in 0.25 ml acetonitrile and a solution of 131 mg of triphenylphosphine in 0.25 ml of acetonitrile were pipetted in a P.M.R. tube which was sealed. No signals originating from 3-endo-bromo-3-exo-chlorocamphor were observed after 24 hrs at room temperature. The tube was then heated at 100° for 50 hrs. P.M.R. spectrum showed the presence of a considerable amount of 3-endo-chlorocamphor. There was no evidence for epimerisation.

REACTION OF 2,5-DIOXOBORNANE WITH n-BUTYLLITHIUM

A. 5-OXOBORNYL ACETATE

From 100 g (0.51 mole) of l-bornyl acetate (Aldrich chemicals) by the oxidation with chromium trioxide following the pro-

B. WITH TRIPHENYL PHOSPHINE

1. In benzene: 3-exo-Bromo-3-endo-chloro-D-camphor (266 mg, 1.0 mmole) was dissolved in 0.2 ml benzene in a P.M.R. tube. A 0.15 ml solution of 262 mg (1 mmole) triphenylphosphine in benzene was pipetted in, the tube sealed and P.M.R. spectrum recorded. A periodic scan was taken of the C-4 proton region. No change was detected after 24 hrs. The tube was then heated at 100° for 50 hrs. Considerable solid deposited leaving a clear yellow supernatant liquid showing in its P.M.R. spectrum complete absence of the starting material.

2. In carbon disulfide: A solution of 266 mg 3-exo-bromo-3-endo-chlorocamphor in 0.2 ml of carbon disulfide and 261 mg of triphenylphosphine in 0.3 ml of carbon disulfide were pipetted in a P.M.R. tube. No sign of epimerisation was observed in the course of 24 hrs.

3. In acetonitrile: A solution of 132.7 mg 3-exo-bromo-3-endo-chlorocamphor in 0.25 ml acetonitrile and a solution of 131 mg of triphenylphosphine in 0.25 ml of acetonitrile were pipetted in a P.M.R. tube which was sealed. No signals originating from 3-endo-bromo-3-exo-chlorocamphor were observed after 24 hrs at room temperature. The tube was then heated at 100° for 50 hrs. P.M.R. spectrum showed the presence of a considerable amount of 3-endo-chlorocamphor. There was no evidence for epimerisation.

REACTION OF 2,5-DIOXOBORNANE WITH n-BUTYLLITHIUM

A. 5-OXOBORNYL ACETATE

From 100 g (0.51 mole) of l-bornyl acetate (Aldrich chemicals) by the oxidation with chromium trioxide following the pro-

cedure given by Malkonen[72] was obtained 39.11 g (36.5%) of crude 5-oxobornyl acetate, b.p. 94-104°/1mm as a yellow oil, tending to crystallise on storage.

P.M.R. spectrum: C-2 exo methine proton 5.08 p.p.m. (ddd), acetoxyl methyl 2.05 p.p.m. (3H, s), other methyls 1.03 p.p.m. (6H, s) and 0.96 p.p.m. (3H, s). (Major component). Several unassigned signals from impurities were present.

B. 5-OXOBORNEOL

Crude 5-oxobornyl acetate (20.0 g, 95.0 mmoles) was dissolved in 100ml of methanol. A solution of 11 g of potassium hydroxide in 10 ml of water was added. The mixture was refluxed for 1 hr., cooled, diluted with 500 ml of water and extracted with diethyl ether to give 8.2 g of a solid which on crystallisation from 60-80° petroleum ether afforded 5.7 g of crude 5-oxobroneol as a brownish crystalline solid.

P.M.R. spectrum: C-2 exo methine proton 4.2 p.p.m. (ddd), methyls 1.01, 0.96 and 0.91 p.p.m. (s). An unidentified impurity, presumably 5-oxo isoborneol, having a one proton multiplet at 3.86 p.p.m. and methyls at 1.1, 0.86 and 0.83 p.p.m. was also present.

C. 2,5-DIOXOBORNANE

The crude mixture of 5-oxobornanols (5.4 g, 32 mmoles) was dissolved in 30 ml of acetone. A solution of 3.2 g of chromium trioxide in 13.5 ml of water and 2.8 ml of sulfuric acid was added dropwise with stirring on an ice bath. After 1 hr in the ice bath and 9 hr at room temperature sulfur dioxide was passedin the mixture till it turned green. The mixture was diluted with water and extracted with diethyl ether. The ether extracts were washed with saturated sodium bicarbonate solution, water and brine, dried,

filtered and ether was evaporated to give 4.8 g of a solid which crystallised from 80-100° petroleum ether to give 3.7 g (69%) of 2,5-dioxobornane as a white solid. A further recrystallisation from 60-80° petroleum ether gave a white camphor like crystalline solid, m.p. 200-202° (lit.[135] 213-214°).

P.M.R. spectrum: Methyls 1.06 p.p.m. (ill resolved d), 0.96 p.p.m. (s). No signal below 3.0 p.p.m.

D. REACTION WITH n-BUTYLLITHIUM

2,5-Dioxobornane (3.32 g, 20 mmoles) in 50 ml of tetrahydrofuran was taken in the direct reactor under nitrogen, n-butyllithium solution (16 ml, 1.6M, 25.6 mmoles) was injected, the mixture stirred at room temperature for 2 hrs and then cooled to -50°. Acetic anhydride (3 ml, 30 mmoles) was injected and the mixture brought to room temperature during 2 hrs while continuously stirred. The mixture was worked up as in the case of the preparation of camphor enol acetate. Removal of the solvent left 4.2 g of the crude product as a yellow oil which was distilled at reduced pressure. A forerun (~ 1.0 ml) was rejected. A pale transparent oil, 2.9 g (69%), b.p. 128-140°/10-12 mm was collected.

P.M.R. spectrum: Vinylic proton 5.50 p.p.m. (d, J = 4 c.p.s.), 5.1 p.p.m. (d, J = 1.5 c.p.s.), acetoxy methyls 2.14 p.p.m. and 2.05 p.p.m. (s) and other methyls 1.18, 1.0 and 0.88 p.p.m. (s).

The crude distillate was judged to be a mixture of 5-oxo born-2-enyl acetate and 2-oxoborn-5-enyl acetate.

REACTION OF NORBORNANONE WITH n-BUTYLLITHIUM

Norbornanone (5.546 g, 50.36 mmoles "norcamphor", Aldrich chemicals) in 200 ml of tetrahydrofuran was taken in the direct

reactor under nitrogen. n-Butyllithium (64 mmoles) was injected and the mixture stirred at room temperature for 30 min, followed by cooling to -50°. Acetic anhydride (10 ml, 98 mmoles) was added and the mixture was stirred for 2 hrs. Work up followed a procedure earlier used for preparing camphor enol acetate to give 6.4 g of a pale yellow oil.

P.M.R. spectrum: Acetoxy methyl 1.98 p.p.m. (s), other methyls 0.93 p.p.m. (m). No signals between 3.5-6.0 p.p.m. were present.

The crude product was distilled giving 4.91 g of a clear colourless liquid, b.p. 118-120°/20 mm. This material gave a green colour with 1% ethanolic ferric chloride solution and its P.M.R. spectrum was identical to the crude product.

A portion of the distillate (2g) was taken up in 50 ml of diethyl ether and extracted several times with a 10% solution of ferric chloride in water till the aqueous phase remained pale yellow in colour (no more green or violet colours). The washings were set aside for regeneration of the 1,3-dicarbonyl compound. The ether solution was further extracted with 10% potassium hydroxide solution, dried, filtered and the ether was evaporated to give 1.922 g (96.1% of the distillate), $\nu_{max}^{CS_2}$ 1730 (C = O) single sharp band, 1254 and 1220 cm^{-1} (C-O-C).

P.M.R. spectrum: Acetoxy methyl 1.98 p.p.m. (s), other methyls 0.95 p.p.m. (m). There was no signal below 3.2 p.p.m.

The product was evidently 2-acetoxy-2-butyl norbornane.

The ferric chloride complex in the aqueous washes was acidified with hydrochloric acid (to pH~1.0), extracted with diethyl ether, ether solution washed with water, saturated brine, dried,

filtered and evaporated to give 34.5 mg (1.73% of the distillate) of 3-acetylnorcamphor, $\nu_{max}^{CS_2}$ 1750 (C=O), 1770 and 1710 cm^{-1} (H-bonded C=O).

P.M.R. spectrum: enolic proton 9.0 p.p.m. (1H, s). C-3 methine proton 3.0 p.p.m. (d), acetyl methyls 2.26 and 2.13 p.p.m. (s).

RELATIVE RATES OF DEBROMINATION OF DIHALOCAMPHORS BY HBr IN ACETIC ACID

An intimate mixture of 3-bromo-3-chlorocamphors (268 mg, 1.01 mmoles) containing equal amounts of either of the epimers and 2 ml of acetic acid saturated with hydrogen bromide were heated in a sealed tube for 10 hrs. The contents which contained free bromine after usual workup gave 260.6 mg of a glassy solid composed of 44.2% of 3-chlorocamphors and 55.8% of epimeric 3-bromo-3-chlorocamphors. P.M.R. spectrum: 2.82 p.p.m. (0.387H), 2.67 p.p.m. (0.613H). Relative rates (computed as first order dehalogenation) 2.2 (the 3-exo-bromoepimer dehalogenating faster).

KINETICS OF DEHALOGENATION OF 3,3-DIHALOCAMPHORS

REAGENTS AND SUBSTRATES - Triphenylphosphine (Eastman organic chemicals white label) was crystallised twice from 95% ethanol and dried under vacuum, m.p. 79-79.5°. Sodium borohydride (B.D.H., L.R.) was used without purification. Tri-n-butyl tinhydride was prepared from tri-n-butyl tin chloride (Alfa Inorganics) following the directions of van der Kirk,[148] et. al., b.p. 85-86°/1.4 mm, and was stored under dry nitrogen. 3-Mono- and 3,3-dihalocamphors were reference samples. 3-exo-Bromo-3-endo-chloro-D-camphor was over 99% pure, m.p. 64-64.5° and 3-endo-bromo-3-exo-chloro-D-camphor was 95 ± 1% pure, m.p. 50-50.5°. Other reagents were analytically pure. Amines were distilled after storing over potassium hydroxide pellets.

SOLVENTS - All solvents used for kinetic runs were dried and distilled before use. Special precaution was taken in the case of ether solvents (dioxane, tetrahydrofuran, etc.) to eliminate traces of peroxides (iodide test). General procedure for removal of peroxides consisted of passage through neutral grade I alumina followed by distillation over lithium aluminium hydride. Alcohols and acetonitrile were Fisher spectral grade: these were dried over activated molecular sieves and freshly distilled before use.

TEMPERATURE CONTROL - Bronwill constant temperature circulator in a well insulated water bath, with a copper spiral for running cold water gave temperature control 0.01° in the range 10-55°. For lower temperatures a heavily insulated Dewar flask with acetone - dry ice and manual control by dry ice addition gave temperature control within ± 2°.

ANALYTICAL PROCEDURE

a. Triphenylphosphine[149]: A stock solution of iodine was prepared

typically by dissolving 1.27 g of iodine in 100 ml of water and 15 g of potassium iodide. Methanol (250 ml) was added and the volume made up to 500 ml with distilled water, and the solution was stored in amber coloured glass bottles. Desired concentrations were prepared by dilution with water and standardisation against sodium thiosulfate solution using starch indicator. A known quantity (A ml) of iodine solution, approximately twice that required for a sample of triphenylphosphine was accurately pipetted into an Erlenmeyer flask containing acetic acid co-solvent. An aliquot (B ml) of triphenylphosphine solution was delivered in this solution which was magnetically stirred. Excess iodine was titrated after 2-3 min with standard sodium thiosulfate solution to starch end point. Let the volume of thiosulfate of normality N required be X ml. A blank was run with A ml iodine, acetic acid and the solvent in which triphenylphosphine was carried. Let the blank require Y ml thiosulfate. The concentration of triphenylphosphine in the aliquot is then $\frac{(Y-X)N}{2B}$ moles litre^{-1}.

b. Estimation of halide ions - The volumetric procedure was based on Volhard method.[150]

Stock solution of Standard silver nitrate was stored in amber coloured glass bottles, diluted to desired strength and each batch freshly standardised against potassium bromide as primary standard. Potassium thiocyanate contained 9.719 g reagent grade material in 1 l solution and stored well protected from light.

The Fe^{3+} reagent was prepared by dissolving 14 g ferric ammonium sulfate in 40 ml of hot water, cooling to room temperature, filtering and making up the filtrate to 50 ml with 6N nitric acid.

For the estimation of halide ions 25 ml of water, 2 ml of 6N nitric acid, 1 ml of Fe^{3+} reagent and exactly 1 ml of 0.1N potassium thiocyanate were taken in an Erlenmeyer flask and the solution stirred magnetically. An accurately measured aliquot (A ml) of the solution containing halide ions was pipetted into the stirring solution of potassium thiocyanate. The deep red coloured solution was titrated with standard silver nitrate till the colour just vanished. A few drops of chloroform towards the end point facilitated visual determination of the colour change. Let the volume of N normal silver nitrate consumed be X ml. A reagent blank omitting the halide ions was carried out under identical conditions requiring Y ml of silver nitrate. The concentration of halide ions in the aliquot is then given by $\frac{(X-Y)N}{A}$ eqv litre^{-1}.

c. Estimation of Sodium Borohydride[151] A stock solution of periodate was prepared from sodium periodate (1.3357 g) dissolved in water and made up to 500 ml to give 0.1N solution. A 25 ml aliquot was pipetted into an Erlenmeyer flask containing 2 g of potassium iodide, followed by 20 ml of 10% sulfuric acid. The liberated iodine was titrated with standard sodium thiosulfate to starch end point. Let X ml of N normal thiosulfate be required for the blank. For assay an aliquot (A ml) of sodium borohydride was pipetted in an Erlenmeyer flask followed by 25 ml of periodate solution. The flask was stoppered and shaken thoroughly for 10 min. A 2 g quantity of potassium iodide and 20 ml of 10% sulfuric acid were then added, the mixture stirred magnetically and the liberated iodine titrated with sodium thiosulfate as before. Let the volume of thiosulfate consumed for the assay be Y ml.

Strength of sodium borohydride is then given by $\frac{(X-Y)N}{A}$ equivalents litre^{-1}, or $\frac{(X-Y)N}{4A}$ moles litre^{-1}.

REDUCTIVE DEHALOGENATION BY TRIPHENYLPHOSPHINE IN METHANOL

A. PRODUCTS

3,3-Dibromo-D-camphor (309 mg, 0.99 mmole) was dissolved in 25 ml of methanol and equilibrated at 25° in the thermostat . A solution of triphenylphosphine (520 mg, 2.06 mmoles) in 25 ml of methanol was also equilibrated at 25° and the two solutions mixed. The mixture was thermostated at 25° for 24 hours and then poured in 500 ml of water and extracted with petroleum ether. The petroleum ether solution was washed with mercuric chloride in acetone, followed by several washings with water, dried, filtered and solvent evaporated to leave a residue of leafy crystalline solid, 226 mg, (97.5%), m.p. 75-75.5°.
The P.M.R. spectrum showed pure 3-endo-bromocamphor (no exo epimer detected.)

Under identical conditions a mixture of 233 mg (1.01 mmole) of 3-endo-bromocamphor and 260 mg (0.99 mmole) of triphenylphosphine in 20 ml of methanol after a period of 24 hours at 25° and work up gave 210 mg (90%) of residue from petroleum ether, m.p. 74-75°, identified as 3-endo-bromocamphor by P.M.R. spectroscopy.

A solution of 266 mg (1.0 mmole) of 3-endo-bromo-3-exo-chloro-D-camphor, and a solution of 233 mg (0.89 mmole) of triphenylphosphine in 100 ml of methanol were equilibrated at -35°, mixed together and left in the -35° bath for 22 hours. The mixture was poured on ~200 g ice, treated with 0.1M iodine solution till a faint yellow colour persisted, extracted with petroleum ether and petroleum ether solution washed with 10% sodium bisulfite sol-

ution, water, brine, dried, filtered and evaporated to give 209 mg of oily liquid. The P.M.R. spectrum showed 3-endo-chlorocamphor and 3-endo-bromo-3-exo-chlorocamphor. None of 3-exo-chlorocamphor was detected.

B. KINETICS OF DEHALOGENATION

Triphenylphosphine (1 mmole) and 3,3-dihalocamphor (1 mmole) were weighed out accurately in two clean dry 100 ml volumetric flasks fitted with glass stoppers. A little less than 100 ml of methanol was pipetted in the flasks and the contents agitated to give homogeneous solutions. The thermostat was set at desired temperature (see procedure) and the reagent solutions thermostated for thermal equilibration for 60 to 90 min. The solutions were brought exactly to the 100-ml mark with previously thermostated methanol, and shaken thoroughly to ensure homogeneous solutions before placing back again in the thermostat. An empty glass stoppered Erlenmeyer flask served as the reaction chamber and was fitted in the thermostat. Equal volumes of reactants were pipetted, after at least once flushing the pipette with the thermostated solution, into the reactor chamber. The solutions were mixed together by agitating the reaction chamber thoroughly at the same time starting the time marker. Initial concentrations in both the reactants were 0.005 moles litre^{-1}.

At suitable time intervals 5-ml aliquots were drawn and pipetted into 5 ml of iodine and 10 ml of acetic acid in an Erlenmeyer flask. The solutions were magnetically stirred and excess iodine titrated against standard thiosulfate. The data were processed for each point by the expression $k_2 = 1/C - 1/C_0 \times 1/t$; where k_2 is in litres mole^{-1} min^{-1}, C_0 is initial concentration

in triphenylphosphine = initial concentration in dihaloketone; C = concentration in triphenylphosphine at time t, in minutes from start.

SUBSTRATE: 3,3-DIBROMO-D-CAMPHOR

15°			6°			-45°		
time min.	C	k2	time min.	C	k2	time min.	C	k2
5	2.5×10^{-3}	52.1	5	2.6×10^{-3}	37.5	30	4.3×10^{-3}	1.3
15	9.5×10^{-4}	56.6	15	1.4×10^{-3}	32.9	60	3.8×10^{-3}	1.2
30	3.3×10^{-4}	94.2	30	7.5×10^{-4}	37.9	90	3.5×10^{-3}	1.1
50	1.0×10^{-4}	196	40	3.5×10^{-4}	53.2	150	2.9×10^{-3}	0.97
60	3.0×10^{-5}	548	60	2.8×10^{-4}	56.2	180	2.7×10^{-3}	0.96

C_0 = 0.005 moles litre^{-1}.

At -45° the solution was not homogeneous. A white precipitate separated out.

REDUCTIVE DEHALOGENATION BY TRIPHENYLPHOSPHINE IN 75% ACETONITRILE

The solvent system 75% acetonitrile was made by mixing 750 ml of acetonitrile, 485 mg of potassium acetate and 250 ml of water.

A. PRODUCTS

Solutions of 3,3-dibromocamphor and triphenylphosphine in the above solvent, each 0.005 M in the reactants were separately prepared and thermostated at 25 ± 0.01°. The two solutions were mixed, the mixture thoroughly shaken and thereafter left in the thermostat. After 24 hours, the mixture was poured in 1 litre of water and extracted 3 times with a total of 200 ml of petroleum ether. The petroleum ether solution was washed, dried, filtered and evaporated to leave a residue of a leafy solid. The P.M.R.

SUBSTRATE: 3-exo-BROMO-3-endo-CHLORO-D-CAMPHOR

$Co \times 10^3 = 5.000$ (25°)			$Co \times 10^3 = 5.130$ (-5°)			$Co \times 10^3 = 4.725$ (-15°)			$Co \times 10^3 = 4.750$ (-25°)		
t min.	$C \times 10^4$	k_2	t min.	$C \times 10^3$	k_2	t min.	$C \times 10^3$	k_2	t min.	$C \times 10^3$	k_2
30	9.81	27.3	30	3.360	3.42	30	3.725	1.89	30	4.20	0.92
45	6.56	29.4	60	2.515	3.38	90	2.625	1.88	90	3.45	0.88
60	4.68	32.2	90	2.015	3.35	120	2.275	1.89	180	2.675	0.91
120	2.18	36.4	180	1.255	3.34	330	1.175	1.93	300	2.050	0.92

SUBSTRATE: 3-endo-BROMO-3-exo-CHLORO-D-CAMPHOR

$Co \times 10^3 = 4.630$ (-5°)			$Co \times 10^3 = 4.675$ (-15°)			$Co \times 10^3 = 4.775$ (-25°)		
t min.	$C \times 10^3$	k_2	t min.	$C \times 10^3$	k_2	t min.	$C \times 10^3$	k_2
30	4.165	0.803	60	3.975	0.63	90	3.925	0.50
60	3.725	0.87	90	3.700	0.62	180	3.350	0.49
90	3.375	0.89	150	3.225	0.64	270	2.925	0.49
120	3.065	0.92	210	2.925	0.60	360	2.625	0.48
150	2.830	0.91	270	2.575	0.64	450	2.375	0.47

spectrum revealed pure 3-endo-bromocamphor (none of exo epimer detected.

A solution of 3,3-dibromocamphor and a solution of triphenylphosphine, each 0.005 M in the reactants were separately prepared in 75% acetonitrile and thermostated at 25 ± 0.01°. Exactly 50 ml of each of the solutions were pipetted in an Erlenmeyer flask fitted in the thermostat. The mixture was briefly agitated, and aliquots were drawn at suitable time intervals for the assay of triphenylphosphine as well as for halide ions. For each point concentration of halide ions was calculated. Disappearance of triphenylphosphine was calculated as a difference of initial concentration of triphenylphosphine and concentration at time t.

t min.	Br^- litre^{-1}	PPh_3 Consumed Moles litre^{-1}
15	1.27×10^{-3}	1.26×10^{-3}
45	1.9×10^{-3}	1.9×10^{-3}
90	2.0×10^{-3}	2.1×10^{-3}

B. KINETICS

About 0.5 mmole each of the haloketone and of triphenylphosphine were accurately weighed in two separate 100-ml volumetric flasks and dissolved in 75% acetonitrile. Volumes were made up to 100 ml after 60-90 min thermal equilibration. An empty glass stoppered Erlenmeyer flask fitted in the thermostat served as reactor. Exactly 50 ml each of the solutions were pipetted in the reactor, the latter agitated vigorously to mix the two solutions, simultaneously starting the time marker. The reaction was followed by periodically drawing aliquots into excess iodine solution and titra-

ting against standard thiosulfate. A reagent blank was run.

For each point the data were processed as

$$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)}$$

where a = initial concentration of triphenylphosphine, b = initial concentration of haloketone and x = fraction of triphenylphosphine consumed. Concentrations are in moles litre^{-1} and time in min.

At 25° + 0.01°.

SUBSTRATE: 3,3-DIBROMO-D-CAMPHOR

a = 2.475 x 10^{-3} moles litre^{-1}

b = 2.509 x 10^{-3} moles litre^{-1}

t min.	x x 10^3 moles litre^{-1}	$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)}$
15	1.238	411
30	1.619	754.8
45	1.875	1228.5
60	1.963	1177.8
75	2.075	1496.4
90	2.137	2481.3

SUBSTRATE: 3-exo-BROMO-3-endo-CHLORO-D-CAMPHOR

a = 2.443 x 10^{-3} moles litre^{-1} b = 2.504 x 10^{-3} moles litre^{-1}

t min.	x x 10^3 moles litre^{-1}	$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)}$
30	0.823	204
60	1.233	400.2
90	1.469	588.6

(cont'd)

t min.	$x \times 10^3$ moles litre^{-1}	$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-x)}$
120	1.645	804.0
195	1.903	1345.5
255	2.007	1734.0
315	2.075	2110.5

SUBSTRATE: 3-endo-BROMO-3-exo-CHLORO-D-CAMPHOR

$a = 2.487 \times 10^{-3}$ moles litre^{-1} $b = 2.512 \times 10^{-3}$ moles litre^{-1}

t min.	$x \times 10^3$ moles litre^{-1}	$\frac{2.303}{(b-a)} \log \frac{a(b-x)}{b(a-z)}$
30	0.257	55.26
60	0.457	102.30
90	0.647	147.33
120	0.817	204.60
180	1.027	284.40
240	1.217	386.40
300	1.367	489.00
390	1.527	627.90

C. EFFECT OF TEMPERATURE ON RATES

At least 6 points were assayed. Second order rate constants, k2, were calculated for each point and average figures are given below. The mean deviation in rate constants was ± 2.5%.

Temp.	DIBROMOCAMPHOR k2	exo-BROMO-endo-CHLORO CAMPHOR k2	endo-BROMO-exo-CHLOROCAMPHOR k2
15	13.6	-	1.65
25	27.3	6.72	2.59

(cont'd)

Temp.	DIBROMOCAMPHOR k2	exo-BROMO-endo-CHLORO CAMPHOR k2	endo-BROMO-exo CHLOROCAMPHOR k2
35	41.8	11.48	2.59
45	-	18.68	4.43
55	-	25.8	6.34

D. EFFECT OF SOLVENTS

Dehalogenation rates for 3,3-dibromocamphor by triphenylphosphine were determined for each of the following solvent systems at 25 ± 0.01° in exactly the same manner as for acetonitrile.

1. 80% Ethanol: Contained 200 ml of absoluteethanol, 50 ml of water and 245 mg of potassium acetate. The second order rate constant from triphenyl phosphine titre at 15 min was 104.8, at 30 min 103.1, at 45 min 100.2 (over 90% reaction). Average k2 of first two measurements = 104 litres $mole^{-1}$ $min.^{-1}$

2. 80% Acetone: Contained 200 ml of dried and freshly distilled acetone, 50 ml of water and 245.3 mg of potassium acetate. Average value of k2, calculated for 6 points, is 2.64 litres $mole^{-1}$ $min.^{-1}$

3. 80% Methanol: A solution of 200 ml of methanol, 50 mg of water and 245.8 mg of potassium was used. The reaction velocity was extremely fast in this system. Titre at 10 min showed over 90% triphenylphosphine consumed. Only the first tiration figure (10 min) was used to calculate k2 = 559 litres $mole^{-1}$ $min.^{-1}$

4. 4 M Acetic Acid: Water (18 g) and 240 mg of potassium acetate were mixed in a 250-ml volumetric flask. The volume was made up by acetic acid. A 15 minute titre showed 96% consumption of triphenylphosphine, giving k2 = 297.

5. 80% Dioxane: Freshly distilled peroxide free dioxane (200 ml), water (50 ml) and potassium acetate (245 mg) were mixed. The reaction velocity was measured from 6 aliquots at 25°. Average $k2 = 0.841$ litres $mole^{-1}$ $min.^{-1}$

E. EFFECT OF TRIPHENYL PHOSPHINE ON 3-endo-BROMOCAMPHOR

1. In 75% acetonitrile: Solutions of triphenylphosphine and 3-endo-bromocamphor in 75% acetonitrile (both 0.01 M) were equilibrated at 25 ± 0.01°. Equal volumes of the reactants were mixed to give 0.005 M initial concentrations in each of the reactants. No change in triphenylphosphine concentration was observed after 6 hours.

2. In Methanol: Identical runs in methanol did not show any triphenylphosphine consumption after 16 hours at 25°.

REDUCTIVE DEHALOGENATION BY SODIUM BOROHYDRIDE

A. PRODUCTS

A 0.0114 M solution of sodium borohydride in 2-propanol and 0.01 M solution of 3,3-dibromocamphor in 2-propanol were thermostated at 25 ± 0.01° for 1 hour. Equal volumes were pipetted in a reactor flask in the thermostat, the solutions were mixed thoroughly and thermostated again. The initial concentrations were thus 0.0057 M in borohydride and 0.005 M in the haloketone. After 5.5 hours 40 ml of the solution was poured in 200 ml of water, acidified with hydrochloric acid and extracted with 100 ml of diethyl ether. Ether solution was washed, dried, filtered and evaporated to give 42 mg brownish crystalline solid. The P.M.R. spectrum showed only 3-bromocamphor (recovery 68%). An aliquot of the reaction mixture was pipetted into an Erlenmeyer flask con-

taining reagents for halide ion estimation. Halide titre was 0.00494 moles litre^{-1}, i.e., 99.8% of one atom halide ion was liberated.

A solution of 3-endo-bromocamphor (initial concentration 0.005 M) and sodium borohydride (0.025 M) in 2-propanol under identical conditions at 25° for 24 hours showed complete absence of halide ions in the tire. Work up as above gave 114.5 mg solid. P.M.R. spectrum showed only 3-endo-bromocamphor and 3-exo-bromocamphor. There was no evidence for carbonyl reduction products. Recovery as 3-bromocamphor was 97.5%.

Previously thermostated solutions of epimeric 3-bromo-3-chlorocamphors and sodium borohydride in propanol were mixed and thermostated at 25 ± 0.01° for 90 min to give an initial concentration in dihalocamphors of 0.02 M and in borohydride of 0.04 normal. The reaction was quenched by pouring in 30 ml 6 N HNO_3. Organic neutral (and acidic) products were extracted with diethyl ether. Aqueous layer was made to 500 ml in a volumetric flask and an aliquot titrated for halide ions giving a concentration of 0.00634 N in halide ions i.e., 32% of 1 equivalent dehalogenation. Ether extract was washed, dried, filtered and evaporated to give 409.8 mg of a semi solid whose P.M.R. spectrum showed a one proton quartet at 4.7 p.p.m., doublet at 4.5 p.p.m. (C-3 methine proton of dihalo hydrin) and recovered epimeric starting material.

A 0.01 M solution of 3,3-dichloro-D-camphor and 0.3 N sodium borohydride in 2-propanol after 12 hours at 25° after work up gave ~ 2% halide ions in aqueous washes. From ether solution 417.9 mg (93.5%) of 3,3-dichloro-2-exo-bornanol as a yellow semi

solid was obtained, $\nu_{max}^{CS_2}$ 3500 cm^{-1} (OH).

P.M.R. spectrum: 1 proton singlet at 2.9 p.p.m. (exchanges with deuterium oxide), a one proton sharp singlet at 4.0 p.p.m. (C-2 methine proton), methyl at 1.25 p.p.m. (3H, s) and at 0.99 p.p.m. (6H, s).

B. REDUCTION OF 3,3-DIBROMOCAMPHOR

A 5 g (16.1 mmole) sample of 3,3-dibromocamphor was treated with 0.8 g lithium aluminium hydride in 40 ml diethyl ether for 1 hour at 0°. Excess reagent was destroyed by carefully adding 1 ml of water. The flocculent white suspension was filtered under suction and filtrate evaporated to give 3.497 g semi solid. P.M.R. spectrum: singlet at 4.1 p.p.m. (from 3,3-dibromohydrin) and considerable monobromohydrin.

The crude mixture (0.8931 g) was treated with 100 ml 0.3 N sodium borohydride in 2-propanol, for 10 hours at 25 ± 0.01°. After this period it was poured in 200 ml of water and extracted with petroleum ether. Petroleum ether extract after drying and evaporation gave 0.723 g solid. P.M.R. spectrum still had the signal at 4.1 p.p.m.

Reduction of 3-endo-bromocamphor: A solution of 2.31 g (10 mmoles) 3-endo-bromocamphor in 150 ml of diethyl ether was treated with 1.5 g of lithium aluminium hydride under reflux for 4 hours. The mass was cooled, 1 ml water added cautiously and the mixture filtered under suction. Evaporation of solvent from the filtrate gave 1.4462 g white crystalline solid, identified as crude borneol (crude yield 93.5%).

P.M.R. spectrum: 4.09 p.p.m. (1H, ddd), 0.86 p.p.m. (9H, s), mat-

ches with the spectrum of 2-endo-bornanol (borneol, Aldrich). 3-endo-Bromocamphor (4 g, 17.3 mmoles) was treated with 0.8 g of lithium aluminium hydride in 40 ml diethyl ether at 0° for 1 hour with stirring, 1 ml water was cautiously added, the mass filtered and ether was evaporated to give 3.764 g (93.2%) of camphor bromohydrin as a white solid, m.p. 66-67° (lit.[107] for similar preparation 67-68°), $\nu_{max}^{CCl_4}$ 3500 cm^{-1} (OH).

P.M.R. spectrum: 4.97 p.p.m. (1H, ddd), 3.79 p.p.m. (1H, dd), 2.25 p.p.m. (1H, s, exchanges with D_2O), Me at 0.98, 0.96 and 0.91 (s). Epimeric purity ~85% of 2-endo-hydroxy-3-endo-bromobornane.

A solution of 1.11 g (4.75 mmoles) crude bromohydrin in 25 ml of ethanol and ~10 g of W4-Raney nickel was stirred at room temperature for 12 hours. Ether (50 ml) was added and the mixture filtered under suction, filtrate washed with 100 ml water (3 portions), dried, filtered and solvent evaporated to give 619.6 mg white solid, m.p. 207-208° (lit.[20] 208.5° for borneol). P.M.R. spectrum matches with commercial borneol. Yield on bromohydrin: 84.5%.

C. KINETICS OF DEHALOGENATION

1. Direct estimation: A solution of 310.4 mg (1 mmole) of 3,3-dibromocamphor in 100 ml 2-propanol was thermostated, concentration 0.01M (solutionA). A solution of sodium borohydride 0.01325M (against standard periodate) in 2-propanol, 0.058 M in triethyl amine, was also thermostated (solution B) at 25 ± 0.01°. Exactly 50 ml of A and B were pipetted in the reactor, mixed vigorously and reaction started. Initial concentration was 0.005 in haloketone and 0.00662M (i.e. 0.0265 N) in borohydride. Period-

ically 10 ml aliquots were drawn in a stirring solution of 20 ml water, 2 ml 6 N nitric acid, 1 ml Fe^{3+} and 1 ml thiocyanate. Halide ions were estimated by titration against standard silver nitrate. Concentration of halide ions at 30, 60, 120, 195, 375, and 510 minutes were 1.08×10^{-4}, 2.7×10^{-4}, 18×10^{-4}, 30×10^{-4}, 35.9×10^{-4}, and 37.8×10^{-4} moles $litre^{-1}$ respectively.

2. Competitive Reaction Approach: A sample of 350.2 mg (1.32 mmoles) of 3-exo-bromo-3-endo-chloro-D-camphor (a: 65.4%) and 180.7 mg (0.705 mmoles) 3-endo-bromo-3-exo-chloro-D-camphor (b: 34.6%) were accurately weighed in a flask, dissolved in 30 ml petroleum ether, solvent evaporated and the residue melted at 60° and cooled to give a homogeneous glass (this operation was done to ensure intimate mixing of the epimers). A portion (~ 200 mg) of the glass was examined by P.M.R. spectroscopy and proportions of the two epimers determined by integrations of C-4 proton as well as methyl signals. Average of 6 integrations gave a = 64.1%, b = 35.9%. A solution of 448.5 mg (1.689 mmoles) of the epimeric mixture was made by dissolving in exactly 50 ml of 2-propanol in an Erlenmeyer flask held in a thermostat at 25 ± 0.01°. A 50 ml 0.62N sodium borohydride solution in 2-propanol, previously thermostated was pipetted, the two solutions were mixed by vigorous shaking and the reactor was placed back in the thermostat. After 60 min the entire mixture was quickly poured in a mixture of 50 ml water, 25 ml nitric acid (6N) with stirring and the resulting mixture extracted with 3 portions of petroleum ether. The organic solution was extracted with 2 x 25 ml water and all the aqueous washes were transferred to a volumetric flask and volume made to

250 ml for estimation of halide ions.

Petroleum ether solution on work up gave 355.8 mg of a yellow solid. P.M.R. spectrum revealed signals from monochlorocamphor, halohydrins and epimeric 3-bromo-3-chlorocamphors. Integration of C-4 proton area gave $\underline{a}_f = 53.5\%$, $\underline{b}_f = 46.5\%$. An aliquot of aqueous washes was titrated by Volhard method. Concentration of halide ions (for reaction mixture) = 0.008517 moles litre^{-1}. Since borohydride was in large excess, the two substrates $\underline{a}$ and $\underline{b}$ can be assumed to undergo independent pseudo first order dehalogenation. Let initial concentration of $\underline{a}$ be $(\underline{a})i$, of $\underline{b}$ be $(\underline{b})i$ and final concentration $(\underline{a})f$ and $(\underline{b})f$ respectively. If k^I and k^{II} represent the rate constants for the debromination of the two substrates, then

$$k^I = \frac{2.303}{t} \log \frac{(a)i}{(a)f}, \quad k^{II} = \frac{2.303}{t} \log \frac{(b)i}{(b)f}$$

Therefore

$$k^I/k^{II} = \log \frac{(a)i}{(a)f} \Big/ \log \frac{(b)i}{(b)f} .$$

The concentrations were calculated as below. Initial epimer concentration = 0.0169M, since $\underline{a}_i = 64\%$, $(\underline{a})i = 0.0169 \times 0.64 = 0.0108$M, similarly $(\underline{b})i = 0.0061$M. Halide ion formed was 0.0085 moles litre^{-1}. Assuming only dehalogenation occurred, concentration of unchanged dihalo epimer = 0.0169 - 0.0085 = 0.0084 M.

Since $\underline{a}_f = 53.5\%$, $(\underline{a})_f = 0.0084 \times 0.535 = 0.0045$ M, $(\underline{b})_f = 0.0039$ M.

$$k^I/k^{II} = \log \frac{(0.0108)}{(0.0045)} / \log \frac{(0.0061)}{(0.0039)} = 1.96$$

DEHALOGENATION BY TRI-n-BUTYL TINHYDRIDE

A. PRODUCTS

3-exo-Bromo-3-endo-chloro-D-camphor, 268 mg (1 mmole), was taken in a 3-neck flask fitted with a rubber septum. A condenser leading to mercury well and the third arm fitted with a glass stopper. Nitrogen was let in through the septum. Diethyl ether (90 ml) was added, and nitrogen flushed in. Tri-n-butyl tinhydride 303 mg (1.08 mmoles) in 10 ml ether was injected, the flask was swirled to ensure homogeneous solution and then fitted back in the thermostat at 25 $\pm$ 0.01°. After 12 hours the mixture was poured in 25 ml of 1N nitric acid, and extracted with water thrice. Ether solution was washed once with saturated brine, dried and evaporated to give 521 mg yellow oil, whose P.M.R. spectrum showed complete absence of 3-bromo-3-chlorocamphors. Only camphor product identified was 3-monochloroepimers, 74.5% endo and 25.5% exo.

A mixture of 270 mg ($\sim$ 1 mmole) of 3-endo-bromo-3-exo-chlorocamphor and 315 mg of tri-n-butyl tinhydride under identical conditions after 210 min reaction period gave 524 mg of a yellow oil, containing 45% monochlorocamphor, 55% 3-endo-bromo-3-exo-chlorocamphor amongst identifiable products in the P.M.R. spectrum. The monochlorocamphors contained 68.8% endo epimer and 31.2% exo epimer.

A mixture of 321.6 mg of tri-n-butyl tinhydride and 311.8 mg (1 mmole) of 3,3-dibromocamphor in 10 hours gave 511 mg yellow oil containing only traces of dibromocamphor. The main product from camphor skeleton was 3-monobromocamphor, 72% endo and 28% exo epimer in the P.M.R. spectrum.

In all the above experiments there was considerable loss of solvent. Kinetic runs were therefore made in cyclohexane. The crude products in all the above cases contained an unidentified impurity having the same retention time as halocamphors in the V.P.C.

B. KINETICS

The reactions were carried out in the assembly described above. To a solution of 1.5571 g (5 mmoles) of 3,3-dibromocamphor in 100 ml of cyclohexane in the reactor under slightly positive pressure of nitrogen were pipetted 50 mls of a 0.1 M solution of tri-n-butyl tinhydride in cyclohexane. The stopper was replaced in the reactor and contents agitated briefly to ensure homogeneous mixing of the reactants. A stop watch was simultaneously started and 25 ml aliquots were drawn at suitable intervals and quickly delivered into a vigorously stirred solution of 25 ml 1 N nitric acid to quench the reaction by destroying the metal hydride. The mixture was diluted with 50 ml petroleum ether, and aqueous layer rejected. The organic solution was washed with water, dried, filtered and solvent evaporated in a tared flask. P.M.R. spectra on the crude residue were run. Extent of reaction was estimated from the relative intensities of C-3 methine proton signals of monohalocamphors and C-4 proton signals of recovered 3,3-dihalocamphors. The intensities were measured either by integration or by cut and weigh technique of traces of these signals. For each run percent reaction was calculated and converted to log (100-% reaction).

Tri-n-BUTYL TIN HYDRIDE AT 25° ± 0.01° IN CYCLOHEXANE

DIBROMOCAMPHOR			exo-BROMO-endo-CHLOROCAMPHOR			endo-BROMO-exo-CHLOROCAMPHOR		
t min.	% RXN	log (100-% RXN)	t min.	% RXN	log (100-% RXN)	t min.	% RXN	log (100-% RXN)
120	17.3	1.917	150	6.86	1.969	120	10.85	1.950
(")	(18)	(1.914)						
180	21.2	1.896	300	12.9	1.940	270	14.4	1.932
270	29.9	1.846	450	16.7	1.920	480	16.6	1.921
(")	(28)	(1.857)						
795	54	1.663	840	35.8	1.801	750	34.6	1.815
(420)	(36)	(1.806)						
(1530)	(65)	(1.544)	1440	48	1.716	1320	41.0	1.771

Figures in brackets are for a duplicate run after 10 days.

DEHALOGENATIONS BY POTASSIUM METHOXIDE IN METHANOL

A. PRODUCTS

3,3-Dibromocamphor 1.24 g (4.00 mmoles) in 25 ml methanol and 25 ml of 0.4 N potassium methoxide in methanol after equilibrating at 25 ± 0.01° were mixed together and thermostated for 8 hours. The reaction mixture was poured in 200 ml water and extracted with 200 ml diethyl ether in 3 portions, ether layer washed once with water and aqueous washes set aside. Ether solution on work up gave 704.7 mg of a yellow oil, (neutral fraction). The entire residue was chromatographed on 30 g neutral grade III alumina. Forerun with 200 ml of petroleum ether gave 543.0 mg (43.7%) white solid, m.p. 58.5-59°, identified by T.L.C. and P.M.R. spectrum as 3,3-dibromocamphor. Elution of the column with 200 ml diethyl ether gave 94 mg yellow oil: $\nu_{max}^{CS_2}$ 1730 cm^{-1} (C = O, broad band). T.L.C. on silica gel plate (60-80°) petroleum ether, ethyl acetate (1:1) gave two spots, R_f 0.6 (~70%) and 0.3 (~ 30% of total).

P.M.R. spectrum: methoxyl signal at 3.68 p.p.m., methyls at 0.75, 1.2, and 1.25 p.p.m. (s, strong) and 0.86, 0.91 and 0.81 p.p.m. (s, weak).

The aqueous extracts set aside earlier were taken in a volumetric flask and volume made exactly 250 ml. A 10 ml aliquot was titrated for halide ions. Total halide were 3.875 mequivalents (i.e. 48.4% for 2 atoms bromine per molecule). A 200 ml aliquot of aqueous extract was acidified with 10 ml concentrated hydrochloric acid and extracted 3 times (total 100 ml) diethyl ether, giving 218.9 mg of a viscous oil. P.M.R. spectrum: acid

proton at 11.6 p.p.m. (s),-OMe at 3.7 p.p.m. (s), and other Me at 0.86 and 1.26 p.p.m. (s).

A 40 ml aliquot of aqueous extract was treated with 20 ml 2,4-DNP reagent. The resulting yellow precipitate was collected and recrystallised from ethanol, m.p. 164.5-166° (lit.[146] 167° for 2,4-DNP of formaldehyde).

B. KINETICS

Solution A, 0.1 N potassium methoxide in methanol, solution B, 1.5553 g (5.0 mmoles) 3,3-dibromocamphor in 100 ml methanol (0.05 M). After thermally equilibrating, 50 mls each of A and B were pipetted in the reactor flask, contents shaken and reactor replaced in the thermostat at 25 ± 0.01°. Aliquots (5 ml) were drawn, pipetted into 50 ml water. Alkali was titrated against 0.01 N nitric acid to phenolphthalein end point. Nitric acid (2 ml, 1 N) was added and halide ions titrated by Volhard method. Two independent runs were carried out. Typically the values were:

Time (min)	15	60	210	450	1000	2490	2820
Base, moles litre^{-1}	0.0626	0.0626	0.0606	0.0507	0.0406	0.03170	0.00248
Halide ion, eq vlitre^{-1}	0.0000	0.0000	0.0018	0.0089	0.0164	0.0230	0.0383

DEHALOGENATIONS BY POTASSIUM ISOPROPOXIDE IN 2-PROPANOL

A. PRODUCTS

3,3-Dibromocamphor (310.5 mg, 1.0 mmole) and 6.5 ml potassium isopropoxide in 2-propanol (0.155 N, 1 m eqv) were heated in a sealed tube at 100° for 1 hour. The tube was cooled, opened, contents taken up in 100 ml water, extracted with 100 ml petroleum

ether, aqueous layer separated, petroleum ether layer washed with 50 ml water and combined aqueous washes were titrated against 0.01N nitric acid to phenolphthalein end point. Alkali titre was 0.014 m eqv and halide ion titre was 0.85 m eqv (alkali consumed 0.986 m eqv, halide ion liberated 0.85 m eqv). An aliquot of aqueous washes gave voluminous yellow precipitate with 2,4-DNP reagent, recrystallised from ethanol, m.p. 118-126°, recrystallised from petroleum ether-ethyl acetate, m.p. 124-125° (lit.[146] 126° for DNP of acetone).. The neutral product in the petroleum ether solution, after drying, filtration and evaporation of the solvent, was 247.1 mg yellow oil. P.M.R. spectrum gave 71% of 3-bromocamphor and 29% of 3,3-dibromocamphor.

B. KINETICS

Exploratory runs showed that considerable potassium bromide precipitated out from the solution, halide ion titre becoming erratic. A modified run was designed. In a series of 5 ml volumetric flasks fitted in the thermostat at 25 ± 0.01°, previously thermostated solutions of reactants were pipetted. In each flask 2 mls 0.1057N potassium isopropoxide in 2-propanol were taken. A 1 ml 0.1M solution of 3,3-dibromocamphor in 2-propanol was then pipetted. Contents of each flask were briefly agitated and the flasks fitted back again in the thermostat. Contents of individual flasks, at desired time, were poured in 50 ml water to quench the reaction, the flask rinsed with 5 ml water and combined aqueous washes titrated against standard 0.01 nitric acid to phenolphthalein end point. The acidic mixture was then titrated against silver nitrate for halide ions. Results for a typical experiment are as

below:

Time (min.)	15	30	60	90	150
Base, moles litre^{-1}	0.05576	0.05372	0.05202	0.04420	0.02414
Halide ions, eqv litre^{-1}	0.00567	0.007167	0.00867	0.0145	0.03083

Initial (15 min) figures for halide ion concentration depended on age of dibromocamphor solutions. Older solutions gave larger figures.

B. COMPETITIVE REACTION APPROACH

A control check with equal proportions of 3,3-dihalocamphors (total concentration 0.01M) and potassium isopropoxide (0.05N) in 2-propanol for 90 min at 25° gave 182 mg of a solid from petroleum ether after work up. P.M.R. spectrum showed only 3-chlorocamphors (50.7%) and chlorobromocamphors (49.3%). There was no trace of monobromocamphor.

3,3-Dibromocamphor (155.7 mg, 0.5 mmoles, A) and 132 mg (0.5 mmoles, B) 3-endo-bromo-3-exo-chloro-D-camphor were dissolved in 50 ml of 2-propanol and thermostated. A 50 ml sample of 1N potassium isopropoxide solution was pipetted, the solutions mixed thoroughly and placed in the thermostat for 75 min at 25 ± 0.01°. The mixture was poured in water and extracted with petroleum ether. The aqueous layer was transferred to a volumetric flask and volume made up to 500 ml. A 50 ml aliquot was titrated for halide ions. Total halide ions in the aqueous extract were 0.645 m eqv. The petroleum ether extract gave 214 mg of a solid whose P.M.R. spectrum revealed it to contain dibromocamphor 15%, 3-endo-bromo-3-exo-chlorocamphor 85%.

Total initial concentration in dihalocamphors = 0.01M, (A)i = 0.005, (B)i = 0.005M.

Final concentration in dihalocamphors = 0.00355M (64.5% dehalogenation, from halide ions).

$(A)_f$ = 0.00355 x 0.15 = 0.00053M, $(B)_f$ = 0.00302M.

Relative rate of decomposition of dibromocamphor (k^I) versus 3-endo-bromo-3-exo-chlorocamphor (k^{111}), i.e.

$$k^I / (k^{III}) = \log \frac{(0.005)}{(0.00053)} / \log \frac{(0.005)}{(0.003)}, \quad k^I/k^{III} = 4.4.$$

Dibromocamphor, 154.9 mg (0.5 mmoles) and 134.7 mg (0.507 mmoles) 3-exo-bromo-3-endo-chlorocamphor in 50 ml 2-propanol and 50 ml 0.1N potassium isopropoxide were mixed and left for 75 min at 25 ± 0.01°. Reaction was quenched by pouring in water and the mixture processed as earlier. Halide ion titre of aqueous washes gave 0.665 m eqv i.e. 66.5% dehalogenation. Residue from petroleum ether was 205.9 mg oil, P.M.R. spectrum of which showed 71.6% monohalocamphors (total of monobromo and monochloro) and 28.4% dihalocamphors. Breakdown of monohalocamphors was monochloro 33.8% (representing percent dehalogenation of 3-exo-bromo-3-endo-chlorocamphor) and monobromo 66.2% (percent dehalogenation of dibromocamphor). (Ai) = 0.0049, (Af) = 0.0005; (Bi) = 0.00507, (Bf) = 0.00283. Relative rate for dibromocamphor (k^I) and chlorobromocamphor (k^{II}), = k^I / k^{II} = 3.87. Relative rates of dehalogenation of two epimers, k^{II}/k^{III} $\frac{4.4}{3.87}$ = 1.13.

C. DEHALOGENATION IN 2-PROPANOL

A 0.1 M solution of 3,3-dibromocamphor in 2-propanol (311.0 mg, 1.0 mmole in 10 ml solution) was stored at room temperature (~25°). A 1 ml aliquot after 12 hours gave 0.023 m eqv halide

ions by Volhard titration, i.e. a total of 0.23 m eqv (23% of 1 equivalent per mole) halide ions were liberated. The solution had attained yellow colour. Chromatography on silica gel plates in 60-80° petroleum ether (350 ml), benzene (150 ml) and chloroform (25 ml) mixture gave 3 spots, Rf. 0.35, 0.18 and nil (spot at origin) respectively. On the same plate 3,3-dibromo camphor had Rf. 0.35, whereas 3-endo-bromocamphor Rf. was 0.15 (i.e. product of dehalogenation was not monobromocamphor).

A 0.1 molar solution of dibromocamphor in 2-propanol and in methanol were prepared at the same time and stored at room temperature. Aliquots (1 ml) were periodically drawn and assayed for acidity as well as halide ions. To the aliquot in an Erlenmeyer flask were pipetted 2 mls of 0.1N sodium hydroxide solution. A drop of phenolphthalein was added and the solution titrated against 0.01N nitric acid till the pink colour disappeared. A reagent blank was also run. Halide ions were estimated as before.

TIME	2-PROPANOL SOLUTION		METHANOL SOLUTION	
	Acid (m eqv)	Halide (m eqv)	Acid (m eqv)	Halide (m eqv)
0.5 hrs	-Nil-	-Nil-	-Nil-	-Nil-
12.3 "	0.032	0.03	- " -	- " -
60.5 "	0.099	0.09	- " -	- " -

The remaining material from 2-propanol solution was poured in 50 ml water, extracted with 3 x 50 ml petroleum ether, ether layer dried, filtered and evaporated leaving behind 181.8 mg oil. P.M.R. spectrum gave signals for 3,3-dibromocamphor (C-4 proton at 2.83 p.p.m.) about 50% and a material containing isopropyl

group identified from one proton multiplet at 5.05 p.p.m. This entire residue was chromatographed on 20 g neutral grade III alumina. Forerun with 100 ml petroleum ether gave 93 mg solid, m.p. 58.5-59° (3,3-dibromocamphor). Elution with 50 ml diethyl ether on evaporation of solvent left 43 mg of a yellow oil. P.M.R. spectrum had 1 proton multiplet at 5.05 p.p.m., a two methyl doublet at 1.25 p.p.m. ($J \simeq 6$ c.p.s.) and other methyl singlets at 1.25, 1.03, 0.98, 0.93 and 0.81 p.p.m. Attempted sublimation of this oil at 100° gave long yellow fibres, m.p. 197-198° (lit.[136] 198° for camphorquinone $\nu_{max}^{CS_2} = 1745, 1757$ cm^{-1} (C = 0), superimposable on the spectrum of authentic camphor quinone sample. Repetition of the above experiment with 1.8056g (5.8 mmoles) dibromocamphor in 60 ml 2-propanol after 140 hours storage at room temperature (protected from light) and identical work up gave 2.37 m eqv halide ions and 1.6675 g yellow oil in neutral petroleum ether extract. Chromatography on 60 g grade III neutral alumina yielded 1.4524 g 3,3-dibromocamphor in petroleum ether forerun (100 ml) and 184 mg yellow oil from diethylether eluate. Attempted distillation yielded two fractions, a front zone of yellow fibres and a colourless oil (97.2 mg), $\nu_{max}^{CS2} = 1720$ cm^{-1} (C = 0).
P.M.R. spectrum of the oil had multiplet at 5.05 p.p.m. (2H), a methyl doublet at 1.25 p.p.m. ($J = 6$ c.p.s.) a methyl singlet at 0.81 p.p.m. (3H). Spin spin decoupling at 5.05 p.p.m. caused collapse of methyl doublet at 1.25 p.p.m. and located two more methyl groups (bornane skeleton) in this region. Tentatively identified as <u>camphor quinone diisopropyl ketal</u>.

A control experiment was run with 0.1 M solution of dibromo-

camphor in t-butyl alcohol and two epimeric chlorobromocamphors in 2-propanol, stored at room temperature and protected against light. After 144 hours the solutions were poured in water and titrated for halide ions. Total halide ions in t-butyl alcohol solution of dibromocamphor were 0.002 m eqv, 3-exo-bromo-3-endo-chloro-D-camphor (in 2-propanol) 0.059 m eqv; 3-endo-bromo-3-exo-chloro-D-camphor (also in 2-propanol), 0.059 m eqv.

DEHALOGENATIONS BY POTASSIUM t-BUTOXIDE IN t-BUTYL ALCOHOL

A. PRODUCTS

A solution of 778.5 mg (2.5 mmoles) 3,3-dibromocamphor in 50 ml t-butyl alcohol was thermostated at 25 ± 0.01° for 1 hour in a 100 ml volumetric flask. The solution of 0.1 M potassium t-butoxide reagent was also thermostated and 50 mls of it were pipetted into the flask containing the dihaloketone. The two solutions were mixed thoroughly, thermostated for 2 hours and thereafter poured in 200 ml of water. The aqueous suspension was extracted with 5 x 50 ml petroleum ether, petroleum ether solution washed once with water, dried, filtered and evaporated to give a neutral fraction, 196.8 mg (34%) of 3-bromocamphors as a white solid. The combined aqueous extracts were acidified with 5 ml 6 N nitric acid and extracted with 3 x 50 ml of diethyl ether, combined ether extract was washed once with water and the aqueous washings set aside for halide ion estimation. The ether extracts (acidic fraction) on work up gave 480 mg of a light yellow oil, crystallising to whitish sticky crystals. P.M.R. spectrum gave a broad singlet at 7.85 p.p.m. (relative area 1 proton, exchanges with D_2O), a doublet at 5.63 p.p.m. (J = 8 c.p.s., 0.44H), singlets at 1.33 p.p.m.

(2H), 1.25 p.p.m. (5H) and 0.93 p.p.m. (2H) (mixture of acids). A sample of 24.3 mg of acid dissolved in 2 ml of 0.2 N sodium hydroxide solution titrated against 0.01 nitric acid gave equivalent weight 248. A solution of 418 mg crude acid in 20 ml ethanol and $\sim$8 g W-2 Raney nickel was held at room temperature for 10 hours. The material was filtered under suction and solvent removed under reduced pressure leaving behind 226 mg of an oil. P.M.R. spectrum showed an exchangeable proton at 8.85 p.p.m., complete absence of signals at 5.63 p.p.m. and a complex methyl region. The aqueous extracts after the removal of acidic fraction in the previous operation were made to 500 ml. Halide ion titration on an aliquot gave 2.65 m equivalents halide ions. To the rest of aqueous extract was added 20 ml 2,4-DNP reagent. A fluffy yellow precipitate separated, this was isolated, and recrystallised from ethanol, m.p. 123-125° (lit.[146] 126° for 2, 4-DNP-derivative of acetone).

DEHALOGENATION BY N-METHYLPIPERIDINE

A. PRODUCTS

In a sealed tube were taken 310 mg (1 mmole) 3,3-dibromocamphor and 1 ml N-methylpiperidine (Aldrich) and the tube heated at 135 $\pm$ 5° for 18 hrs. After cooling and opening of the tube the contents (a thick brown tar and a clear light yellow supernatant liquid) were triturated with water and petroleum ether and transferred to a separating funnel. The mixture was extracted with petroleum ether, and ether solution washed with water, 50 ml 1 N sulfuric acid and water in that order. Aqueous washes were set aside. The organic solution was dried, filtered and

evaporated giving 205.2 mg (89%) of 3-monobromocamphors as a yellowish solid. The aqueous extracts were made up to 250 ml. A 10 ml aliquot gave 0.04 m eqv halide ions, i.e. 1 m eqv in total aqueous washes.

The above experiment was repeated with 620.3 mg (2.0 mmoles) 3,3-dibromocamphor and 1 ml N-methylpiperidine in a sealed tube at 135° for 12 hours. The tube was cooled, opened and the contents dispersed in 100 ml diethyl ether in several portions and filtered. The residue was dissolved in 10 ml chloroform and then poured in 100 ml petroleum ether forming a suspension of sticky brown mass. The material was filtered through a sintered funnel, and the two filtrates combined, and washed with 3 x 5 ml 1 N nitric acid, and worked up to give 430.8 mg (95%) yellowish solid identified as 3-monobromocamphors. The brown sticky residue on the sintered funnel was dissolved in chloroform and the solvent was evaporated leaving behind 493.2 mg brown tar. $\nu_{max}^{CHCl_3}$ = 3300-3400 (N-H), 2400-2600 ($H\text{-}\overset{+}{N}R_3$) and 1600 cm^{-1} (C = N). P.M.R. spectrum: 7.53 p.p.m. (1H, t) a broad band centred at 3.33 p.p.m. (6.5 H), 2.9 p.p.m. (3H, s) and another broad band centred at 1.91 p.p.m. (10 H).

An aqueous solution of the material gave halide ion test. A control experiment revealed that at 135° dehalogenation of 3,3-dibromocamphor in N-methylpiperidine is complete in less than 5 minutes.

A solution of 1 g (3.2 mmoles) 3,3-dibromocamphor in 5 ml N-methylpiperidine started turning hazy 15 min after preparation and storage at room temperature protected from light. Fine white needle shaped crystals were detected. After 42 hours the mass was

diluted with 50 ml diethyl ether and ether decanted off leaving behind a gelatinous crystalline solid which was washed 10 more times with dry ether in 10 ml lots and dried in vacuo for 1 hour, giving 13.7 mg of a white solid.

P.M.R. spectrum: 8.66 p.p.m. (2H, s), 3.25 p.p.m. (4H, m) and a broad band centred at 1.91 (6 H). A small quantity (0.2 mg) material was dissolved in 0.1 ml nitric acid and gave positive bromide ion test. Another sample (13.5 mg) was treated with 11.5 mg sodium borohydride in 0.2 ml methanol. A yellow solution was formed. The material was diluted with 25 ml anhydrous diethyl ether and filtered. Filtrate was set aside and the funnel was washed with 10 ml water, acidified with 5 ml of 1 N nitric acid and the aqueous washings titrated with silver nitrate under Volhard conditions giving 0.076 m eqv halide ions. Allowing 1 bromide ion per molecule, molecular weight of the immonium bromide = 177.5 (N-methylene piperidinium bromide, $C_6H_{12}NBr$, M = 178).

Diethyl ether was evaporated from the filtrate set aside earlier and the residue subjected to T.L.C. on a silica gel plate (chloroform, ethyl acetate 1:1), Rf., identical to that of N-methylpiperidine.

In diethyl ether solution 1 g (3.2 mmoles) dibromocamphor and 5 ml N-methylpiperidine in 40 hours storage at room temperature gave a sizeable precipitate. Ether was decanted off and the resulting residue washed several times with dry diethyl ether, dissolved in chloroform and solvent removed under vacuum leaving behind 691.9 mg yellowish semi solid.

P.M.R. spectrum signals at 6.43 p.p.m. (broad s), 3.28 p.p.m. (t)

2.88 p.p.n. (s) and 1.96 p.p.m. (centre of broad band).

B. KINETICS

A solution of 313.9 mg (1.01 mmoles) 3,3-dibromocamphor in 5 ml freshly distilled acetonitrile was prepared and the container (10 ml glass stoppered flask) thermostated for 1 hour at 25 ± 0.01°. A lot of N-methylpiperidine was also thermostated and 5 ml of the reagent was accurately pipetted into the solution of dibromocamphor, contents mixed thoroughly and the flask replaced in the thermostat. At suitable intervals 1 ml aliquots were drawn into 30 ml 1 N nitric acid in an Erlenmeyer flask followed by Volhard titration. A reagent blank omitting dihalocamphor was also run. Equivalent of halide ion liberated were calculated.

TIME (MIN)	HALIDE IONS m eqv	$2.303 \log \frac{a}{a-x}$
60	0.02	2.01×10^{-2}
180	0.06	6.70×10^{-2}
300	0.105	11.1×10^{-2}
420	0.145	15.55×10^{-2}
540	0.170	18.42×10^{-2}
660	0.185	20.3×10^{-2}

The data were processed as a pseudo first order reaction by conversion to $2.303 \log \frac{a}{a-x}$ where a is initial concentration in dihaloketone and x is fraction of reaction. A plot against t is fairly linear till about 14% reaction, giving $t_{\frac{1}{2}}$ = 1860 min. The latter part is asymptotic.

A solution of 306.8 mg (0.98 mmole) dibromocamphor was prepared in a 5 ml volumetric flask in freshly distilled N-methyl-

piperidine. In 6 glass tubes 0.5 ml of the solution was accurately pipetted, thus each tube held 30.68 mg of dibromocamphor. The tubes were sealed and then immersed all at once in an oil bath adjusted at 60 ± 0.05°, marking the zero time. At suitable intervals one tube was taken out, quickly chilled in running cold water, ice-salt bath, opened and 10 ml 1N nitric acid introduced. The contents were rinsed into an Erlenmeyer flask using several small portions of water and titrated for halide ions. A blank was run with the solution before immersing in the 60° bath.

TIME min.	HALIDE IONS m eqv	% RXN	log (100-%RXN)
60	0.0425	21.5	1.895
90	0.0570	28.8	1.852
120	0.0675	33.9	1.820
150	0.0810	41.0	1.771

Infinity titre was done on two tubes held at 60° for 72 hours. After cooling the tubes were opened, contents were taken up in 50 ml 1N nitric acid and extracted with 50 ml diethyl ether. The ether solution on work up gave 24.3 mg residue whose P.M.R. spectrum had signals at 3.58 p.p.m. (s, broad band), 1.13, 1.08, 0.98 and 0.95 p.p.m. No trace of 3-bromocamphors was detected. The aqueous washes on titration gave 0.3755 m eqv halide ions. The total dihaloketone in two tubes was only 0.1975 mmoles indicating that both halogen atoms came from the same molecule.

A competitive reaction approach was designed. A uniform mixture containing 266 mg (1 mmole) 3-exo-bromo-3-endo-chlorocamphor and 265.5 mg (1 mmole) 3-endo-bromo-3-exo-chlorocamphor was pre-

pared. In a sealed tube were taken 266.5 mg (1 mmole) dihalo epimeric mixture and 100.2 mg (1.01 mmoles) N-methylpiperidine. The mixture was heated at 140° for 5 min. After cooling the tube was opened, contents taken up in 40 ml 1N nitric acid and extracted with 50 ml petroleum ether. The aqueous layer was drawn off and ether solution was washed with 2 x 25 ml water. The aqueous washes were made to 100 ml in a volumetric flask. Petroleum ether layer was dried, filtered and evaporated leaving 251 mg residue whose P.M.R. spectrum gave 3-exo-bromo-3-endo-chloro-epimer 49.5%. A 25 ml aliquot was drawn from aqueous extract and gave 0.064 m eqv total halide ions representing 6.4% dehalogenation on 1 eqv halide ions per mole basis. The relative rates of dehalogenation of the 3-exo-bromo-3-endo-chloro epimer (k^{I}) vs the other epimer (k^{II}) were calculated as $k^{I}/k^{II} = 1.29$. A repetition of the above experiment gave $k^{I}/k^{II} = 0.96$.

REDUCTIVE DEHALOGENATION BY PYRIDINE

A solution of 618.8 mg (1.99 mmoles) 3,3-dibromocamphor in 1 ml pyridine, in a sealed glass tube was heated at 135° for 50 hours. The mass turned dark brown. After cooling and opening the tube the contents were diluted with 100 ml anhydrous diethyl ether, depositing a brown flocullent precipitate. The mass was filtered in a sintered glass crucible under suction and residue on the funnel washed with ether and dried, leaving behind 55.1 mg (17%, pyridinium hydrobromide) as a light brown solid. The ether filtrate was washed with 5 x 25 ml 1N nitric acid followed by 3 x 25 ml water, saturated brine, dried, filtered and evaporated leaving behind 590 mg yellow solid whose P.M.R. spectrum

showed it to be largely 3,3-dibromocamphor with 10% 3-monobromocamphor. Recovery of dibromocamphor = 80% (corrected for monobromocamphor). Pyridiniumhydrobromide was identified by P.M.R.

REDUCTIVE DEHALOGENATION WITH s-COLLIDINE

A. PRODUCTS

Several experiments were carried out. In a typical experiment 1.2696 g (4.095 mmoles) of 3,3-dibromocamphor and 2.62 ml (2.38 g, 19.6 mmoles) of distilled s-collidine in a sealed glass tube were heated at 136 ± 2° for 117 hrs. The mass turned dark black semi solid in appearance. The tube was cooled and opened. The contents were triturated in 50 ml of dry petroleum ether, filtered and the filtrate was set aside. The portion of the tube containing black solid and the filter paper were taken in a Soxhlet thimble and extracted with 100 ml diethyl ether for several hours (~ 10 runs). The ether solution was combined with petroleum ether filtrate and the combined solution was washed with 0.1N nitric acid (3 x 25 ml), dried, filtered and evaporated to give 660.3 mg neutral solid (ether soluble). The solid on the Soxhlet thimble still had some ether soluble residue entrapped. This was isolated by Soxhlet extraction with chloroform (100 mls, 20 runs), concentrating the deep violet brown solution to ~ 10 mls and pouring in 100 ml petroleum ether. A violet brown solid precipitated out. The petroleum ether was filtered and the filtrate washed with dilute nitric acid, dried, filtered and evaporated leaving 179.5 mg solid. The combined weight of the two neutral, petroleum ether soluble, acid insoluble solids was 839.8 mg. T.L.C. on silica gel plate (petroleum ether 60-80°, benzene, chloroform

system, 250:150:25) gave only two spots. The main product, Rf. 0.3, was identical with 3-endo-bromocamphor and was about 90% from intensity of the spot. The other product had Rf. 0.15. The crude residue was chromatographed through 120 g of neutral grade III alumina. Elution with 3 litres petroleum ether gave 760.1 mg (3.28 mmoles, 80.3%) 3-monobromocamphors identified by P.M.R. spectroscopy and T.L.C.

The solid remaining behind after reprecipitation from petroleum ether was dissolved in dry chloroform, filtered, and solvent evaporated to give 892.6 mg (4.41 mmoles) of s-collidinium hydrobromide as a violet-brown crystalline solid, recrystallised from chloroform, m.p. 260-270° (decomposes), $\nu_{max}^{CHCl_3}$ 3400, 3250 (N-H), 2500-2800 ($H\text{-}\overset{+}{N}R_3$) and 1630 cm^{-1} (Ar C = C).
P.M.R. spectrum: 14.53 p.p.m. (1H, s), aromatic H 7.48 p.p.m. (2H, s), Me 2.95 p.p.m. (6H, s) and 2.6 p.p.m. (3H, s). (matched the spectrum of an authentic sample of s-collidinium hydrobromide).

Anal. calculated for $C_8H_{12}NBr$ (202.1) C, 47.5; H, 5.98; N, 6.92; Br, 39.6; found C, 47.29; H, 6.02, N, 7.04 and Br, 40.25. The Soxhlet thimble had 100 mg of a black intractable solid powder, insoluble in water, trifluoroacetic acid, acetonitrile, dimethyl sulfoxide, dimethyl formamide and conc. sulfuric acid.

Anal. Found C, 65.03, H, 6.10, N, 7.60 and Br 21.78.

The acidic-aqueous washes in previous fractionations were combined, made strongly alkaline with 6N potassium hydroxide, and extracted with 5 x 60 ml diethyl ether. The ether extracts were washed once with saturated brine, dried, filtered and evaporated, giving 1.006 g (8.45 mmoles) of s-collidine as a yellow oil, iden-

tified by P.M.R. spectroscopy.

A solution of 233.1 mg (0.87 mmole) 3-bromo-3-chlorocamphors (epimeric ratio 1:1) in 486.2 mg (4 mmoles) s-collidine in a sealed tube were heated at 135° for 37 hours. The tubes were cooled, opened and contents triturated in 50 ml of petroleum ether, the ether extract was washed several times with 0.1N nitric acid, dried, filtered and evaporated leaving 189 mg semi solid, P.M.R. spectrum of which showed presence of 3 methine signals from 3-monochlorocamphors and C-4 proton signals from 3-bromo-3-chlorocamphors, relative ratio 19:81 respectively. The intensities of C-4 proton signals from the two epimer 3-bromo-3-chlorocamphors were in the ratio of 50:50.

BROMINATION OF 3-CHLOROCAMPHOR BY BROMINE CATALYSED BY HYDROGEN BROMIDE

In a sealed glass tube 373.2 mg (2 mmoles) of 3-endo-chlorocamphor, 2 ml of acetic acid, 0.15 ml (450 mg, 2.8 mmoles) of bromine and a drop of acetic acid saturated with hydrogen bromide were heated for 1 hr at 110°. The tube was cooled, opened and worked up as usual to give 493.6 mg (90%) of a glassy solid. The crude product contained 8.1% of unchanged starting material.

P.M.R. spectrum: 2.82 p.p.m. (0.393H), 2.68 p.p.m. (0.607H).

DEUTERATION OF CAMPHOR LITHIUM ENOLATE

A solution of 7.6 g (50.0 mmoles of D (+) camphor in 200 ml anhydrous tetrahydrofuran was taken in the upper chamber of the reverse addition assembly. The lower chamber contained 4 ml of acetic acid -d_4 and 2 ml of deuterium oxide. Both chambers were flushed with dry nitrogen. n-Butyllithium (40 ml of 1.6M, 64 mmoles) was injected in the upper chamber at room temperature and stirred for 30 min. The solution of camphor lithium enolate was then added dropwise to the contents of the lower chamber which were stirred magnetically. After 1 hr, stirring was stopped and the assembly disconnected. The contents of the lower chamber separated in two phases, a white jelly sticking to the walls of the chamber and a clear colourless liquid. The liquid was decanted off, diluted with 500 ml of petroleum ether, dried over anhydrous magnesium sulfate, filtered and the solvent removed to leave behind 6.959 g (91%) crude camphor-d_1 as a slightly wet, white solid with a faint odour of acetic acid. A 4 g lot of the crude material was sublimed giving 3.56 g flowery white crystalline solid.
P.M.R. (Plate 1) Methyls at 0.95, 0.91 and 0.84 p.p.m. (s). Mass spec. Camphor do 3.4%, d_1 96.6%, d_2 0.0, major peaks at m/e 153, 110, 108, 95, 83, 82, 81 and 69.

ISOBORNEOL-3-d_1 - A solution of 2.34 g (15.3 mmoles) crude camphor 3-d_1 from the above preparation in 100 ml dry diethyl ether was treated with 1 g lithium aluminium hydride under reflux for 12 hrs. The mixture was cooled, 10 ml of water was cautiously added, and the resulting voluminous precipitate was filtered under suction. The residue on the filter was washed several times with diethyl

ether and the combined filtrate was dried, filtered and solvent evaporated to leave 2.28 g (14.7 mmoles, 96%) crude isoborneol -3-d_1 as a waxy white solid.

P.M.R. spectrum: (Plate 8) 2.35 p.p.m. (1H, d, J2HN3HN = 8 c.p.s.), 2.46 p.p.m. (s, from 0H), Me 1.0, 0.9 and 0.81 p.p.m. (s). (A feeble signal arising from isoborneol- d_0 appeared at 3.56 p.p.m. giving lower limit for isoborneol-3-exo-d_1=80%).

PROTONATION OF CAMPHOR-3-d_2 LITHIUM ENOLATE

A. CAMPHOR-3-d_2

3,3-Dibromocamphor (25.05 g, 81.0 mmoles) was taken in 50 ml of anhydrous dioxane. Acetic acid-d_4 (15 ml) was added and the solution heated on a steam bath with stirring. Zinc powder (15 g, B.D.H. Analar) was added in small amounts. After 2 hrs the mixture was cooled, 200 ml petroleum ether was run in and stirring continued for 1 hr. Deuterium oxide (2 mls) was added. After 10 more minutes of stirring the mixture was extracted with water, petroleum ether layer dried over sodium sulfate, filtered and the solvent distilled to give 11.36 g (73.6 mmoles, 91%) crude camphor-3-d_2 as a white solid which was sublimed to give 11.05 g white feathery crystalline solid, m.p. 177-178° (cap.).

P.M.R. (Plate 1): Me 0.95, 0.91 and 0.84 p.p.m. (s). No signal at 2.5 p.p.m. Mass spec. camphor-d_2=83.5%, d_1=16.5%, d_0=0.00%.

B. ISOBORNEOL-3-d_2

Camphor-3-d_2 (1.087 g, 7.05 mmoles) in 50 ml of dry diethyl ether was treated with 1 g lithium aluminium hydride under reflux for 10 hrs. After cooling the mixture was worked up as before to give 1.075 g (6.9 mmoles, 97.9%) crude isoborneol-3-d_2 as a white

powdery solid.

P.M.R. (Plate 8) 3.53 p.p.m. (1H, s), Me 1.0, 0.9 and 0.81 p.p.m. (s).

C. CAMPHOR-3-endo-d_1

A solution of 7.58 g (49.1 mmoles) camphor-d_2 in 200 ml of anhydrous tetrahydrofuran was taken in the upper chamber of the reverse addition assembly. The lower chamber contained 10 ml acetic acid and 25 ml water. n-Butyllithium (40 mls of 1.6M solution, 64 mmoles) was injected at room temperature in the upper chamber. After 1 hr, the contents of the upper chamber was transferred dropwise to the acetic acid solution in the lower chamber which was stirred magnetically. The assembly was disconnected and the reaction mixture taken up in 100 ml of petroleum ether and washed with water. The petroleum ether layer was dried, filtered and distilled to leave behind 7.05 g white semi solid. Fractional sublimation did not give pure camphor-d_1.

The above experiment was repeated. From 1.535 g (9.95 mmoles) camphor-3-d_2 in 40 ml of tetrahydrofuran and 14.7 ml of 1.36 M (20 mmoles) n-butyllithium, followed by reverse addition to 5 ml acetic acid and 20 ml of water, after work up was obtained 1.64 g of a semi solid mass. T.L.C. on silica gel (petroleum ether 60-80° - ethylacetate 35:65) gave 5 spots, Rf 0.8, 0.62, 0.38, 0.09 and 0.02 respectively. The total intensity of the spot with Rf 0.8 was $\sim$70% and corresponded to camphor. The next intense spot had Rf 0.62 (approximately 25%) and the rest of the spots amounted to about 5%.

V.P.C. of the crude product on a column of 1% DEGS supported

on chromosorb P at 120° gave 3 peaks with retention time 2.6, 3.1 and 7-11 min. The peak with 3.1 min retention time corresponded with camphor and its relative proportion was ~75%.

Attempted chromatographic purification of 1.6 g of crude product on 60 g silica gel gave from 200 ml petroleum ether and 200 ml diethyl ether: petroleum ether (1:19), 382 mg of an oily liquid.

P.M.R. 5.03 p.p.m. (t, J = 7 c.p.s.), Me 0.96, 0.90, 0.86, 0.85 and 0.73 p.p.m. (s). Mixture, containing ~50% of camphor-d_1.

Further elution with 200 ml diethyl ether petroleum ether (1:19) gave 900 mg of a white solid which was sublimed (camphor-3-endo-d_1.

P.M.R. (Plate 1): Me 0.95, 0.91 and 0.84 p.p.m. (s). Mass spec. Camphor-d_o=6.1%, d_1=93.9%, d_2=0.0%. Major peaks at m/e 153, 110, 108, 95, 83, 82 and 69.

D. REDUCTION TO ISOBORNEOL-3-d_1

The sublimed sample (250 mg, 1.63 mmoles) of camphor-3-endo-d_1 in 50 ml of anhydrous diethyl ether was reacted with 500 mg of lithium aluminium hydride for 10 hrs under reflux. After cooling, 1 ml of water was added and the mixture was worked up as described earlier leaving 242 mg (1.56 mmoles, 95.5%) of crude isoborneol-3-d_1 as a white solid.

P.M.R. (Plate 8): 3.6 p.p.m. (s), Me 1.01, 0.9, 0.86 and 0.83 p.p.m. (s). (mixture of 2-bornanols containing ~10% of borneol-3-d_1). At amplitude 10X signal from 3-methine proton of borneol was observed at 4.0 p.p.m. (d, J = 9 c.p.s.). Approximately 90% of isoborneol-3-endo-d_1.

ENOLISATION OF CAMPHOR-3-exo-d_1 - A solution of 1.25 g (8.16 mmoles) camphor-3-exo-d_1 in 40 ml of dry tetrahydrofuran was taken in the upper chamber of the reverse addition assembly. The lower chamber contained 3 ml (30 mmoles) of acetic anhydride in 10 ml dry tetrahydrofuran stirred magnetically. Through the rubber septum in the upper chamber, 14 ml of 1.35M (19 mmoles) n-butyllithium was quickly injected while the mass was stirred vigorously under nitrogen. After 1 hour, the contents of the upper chamber were added dropwise to the stirring mixture in the lower chamber. The mixture was stirred for 1 hr, 10 ml water was added, the assembly was disconnected and the mixture extracted with 100 ml of petroleum ether. The petroleum ether extract was washed with saturated sodium bicarbonate (5 times), water (3 times), dried, filtered and solvent distilled off leaving behind 1.63 g yellow liquid. P.M.R. spectrum: vinylic proton at 5.55 p.p.m. (d, J = 3.5 c.p.s.), D-4 proton at 2.3 p.p.m. (t), acetoxy methyl at 2.1 p.p.m. (s), and other methyls at 0.93 and 0.75 p.p.m., both singlets from camphor enol acetate. Feeble methyl signals at 0.88 and 0.83 p.p.m. from camphor. Relative area of vinylic proton (5.55 p.p.m. signal) versus total of acetoxy methyl and C-4 proton (4 protons) is 1:10.93. Enol acetate d_o = 36.5%, d_1 = 63.5%.

The above experiment was repeated. A solution of 1.3 g (8.5 mmoles) camphor-3-exo-d_1 in 10 ml of tetrahydrofuran was injected into a solution of 14 ml of 1.35M (19 mmoles) n-butyllithium in 40 ml of tetrahydrofuran contained in the upper chamber of reverse addition assembly while the mass was vigorously stirred under nitrogen. After the addition the mass was stirred for 30 min and then added to a solution of 3 ml (30 mmoles) of acetic

anhydride in 10 ml tetrahydrofuran magnetically stirred in the lower chamber. The product was worked up as before giving 1.66 g of a yellow oil. P.M.R. spectrum of the crude oil gave camphor enol acetate d_o = 53.2%, d_1 = 46.8%.

ENOLISATION OF CAMPHOR-3-endo-d_1 - A solution of 1.267 g (8.2 mmoles) camphor-3-endo-d_1 in 50 ml of dry tetrahydrofuran was taken in the upper chamber of reverse addition assembly under nitrogen. After 20 min, 14 ml of 1.35M (19 mmoles) of n-butyllithium was injected all at once, and the mixture added to the solution of 3 ml (30 mmoles) acetic anhydride in 10 ml of tetrahydrofuran with magnetic stirring in the lower chamber. The reaction mixture was subjected to work up as described for camphor-3-exo-d_1, giving 1.645 g yellow oil as the product.

P.M.R. spectrum: vinylic proton at 5.55 p.p.m. (d, J = 3.5 c.p.s.), C-4 proton at 2.3 p.p.m. (t), acetoxy methyl 2.1 p.p.m. (s) and other methyls at 0.93 and 0.75 p.p.m., both singlets from camphor enol acetate, methyls at 0.88 and 0.83 p.p.m. (singlets) from camphor. Relative area of vinylic proton versus acetoxy methyl gave camphor enol acetate d_o = 12%, d_1 = 88%.

The crude product, 1.6 g, was chromatographed on 100 g of neutral grade III alumina. Elution with 250 ml of petroleum ether gave 930 mg camphor enol acetate (d_o and d_1) free of camphor and other impurities. Integration of vinylic proton against acetoxy methyl and C-4 proton gave camphor enol acetate d_o = 16.3 $\pm$ 0.8% and d_1 = 83.7 $\pm$ 0.8%.

CHLORINATION OF CAMPHOR LITHIUM ENOLATE - Camphor 1.52 g (10 mmoles) in 50 ml of dry tetrahydrofuran was taken in the upper

chamber of reverse addition assembly. After 20 min stirring under nitrogen, 8.0 ml of 1.6M (12.8 mmoles) of n-butyllithium was injected and stirring continued for 1 hour. In the lower compartment 20 ml of 1.25M (25 mmoles) chlorine in 50 ml of petroleum ether was stirred with a magnetic stirrer. The enolate in the upper compartment was added dropwise to the chlorine solution. The operations were carried out under protection from direct light. After 5 minutes contents of the lower chamber were poured in 250 ml water. The aqueous layer was faintly acidic. Chlorine was detected in the organic phase which was washed with saturated potassium acetate solution, dried and filtered. After evaporation of the solvent the residue, 1.914 g yellow oil was examined by P.M.R. spectroscopy. The C-3 exo-methine of 3-endo-chlorocamphor appeared at 4.45 p.p.m. (dd) and 3-endo-methine proton of 3-exo-chlorocamphor as a sharp singlet at 3.90 p.p.m. (s). Methyl groups at 1.06, 0.96, 0.9 and 0.83 p.p.m. (all singlets). There was considerable absorption between 4.3-3.3 p.p.m. Relative intensities of 3.9 p.p.m. signal and 4.45 p.p.m. signal were 75.6% and 24.4% respectively from cutting and weighing of traces.

BROMINATION OF CAMPHOR LITHIUM ENOLATE - Procedure was identical to that used for chlorination. A solution of 1.53 g (10 mmoles) camphor in 50 ml dry tetrahydrofuran was reacted with 8 ml, 1.6M (12.8 mmoles) of n-butyllithium under nitrogen for 1 hr at room temperature. The solution of enolate was added in a reverse manner to a mixture of 1.5 ml (4.5 g, 28 mmoles) bromine in 100 ml of petroleum ether with stirring. Work up gave 2.4 g of a yellow oil. P.M.R. spectrum had a signal at 4.65 p.p.m. (dd, 3-exo

methine proton of 3-endo-bromocamphor), 4.08 p.p.m. (s, 3-endo methine proton of 3-exo-bromocamphor) and methyls at 1.13, 1.09, 0.96, 0.91 and 0.83 p.p.m. (all singlets). Some signals between 3.33-4.60 p.p.m. Relative area of 4.65 p.p.m. signal 29.9%, 4.08 p.p.m. signal 70.1%.

ACID CATALYSED BROMINATION OF 3-CHLOROCAMPHOR - A solution of 372 mg (1.99 mmoles) of 3-endo-chloro-D-camphor in 5 ml of trifluoroacetic acid was taken in a glass tube and saturated with hydrogen bromide gas. Bromine (0.03 ml, 0.56 mmoles) was added and the tube sealed. After heating at 102 ± 2° for 50 hrs, the tube was cooled, opened and contents poured in 50 ml water. The mixture was extracted with petroleum ether to give 354 mg white crystalline solid, containing 94.5% 3-monochlorocamphor and 5.45% epimeric chlorobromocamphors.

HYDROGENBROMIDE CATALYSED BROMINATION OF D-CAMPHOR (IN EXCESS BROMINE)

D (+) camphor (1.52 g, 10 mmoles), 2.5 ml (7.5 g, 46.9 mmoles) bromine, 5 ml acetic acid and 1 ml fuming hydrobromic acid were heated on a steam bath ($\simeq$100°). Aliquots were drawn periodically, pipetted into 50 ml saturated sodium acetate solution and extracted with petroleum ether. The ether solution was washed with 10% sodium bisulfite solution to destroy excess bromine, followed by water, dried, filtered and solvent evaporated. The recovered crude product was examined by P.M.R. spectroscopy. An aliquot after 1 hr showed in the P.M.R. spectrum of the crude product some camphor and 3-monobromocamphors. The ratio of 3-methine proton signals from bromocamphors gave exo-bromoepimer 57.8% and endo-bromoepimer 42.2%.

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