Isomerization of Carvone Tribromides. Hydrohalide-Catalyzed Elimination and Readdition

JOSEPH WOLINSKY, JAMES J. HAMSHER,[1a] AND ROBERT O. HUTCHINS[1b]

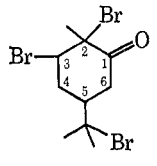
Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received April 22, 1969

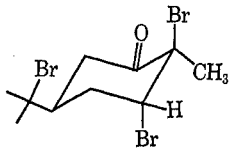
Addition of bromine to carvone hydrobromide (II) affords *trans*-carvone tribromide, I. Equilibration with hydrogen bromide in acetic acid at 0° converts I into a mixture of 45% I and 55% *cis*-carvone tribromide, III. The isomerization involves the exclusive exchange of a substituent (Br, Cl, or OH) β to the carbonyl group and is specifically catalyzed by hydrohalides. The reaction requires the presence of the carbonyl group and the α bromine atom and does not proceed with α-chloro derivatives. The transformations of *cis*-III and *trans*-I occur many times faster with hydrogen bromide than with hydrogen chloride. The rate of reaction of various derivatives isomeric at C-3 follows the order 3-axial bromine > 3-equatorial bromine $\gg$ 3-axial chlorine $>\gg$ 3-equatorial chlorine. A hydrohalide-initiated elimination followed by a hydrohalide-catalyzed readdition of halogen satisfactorily accounts for these transformations.

dl-Carvone tribromide, mp 76°, was first prepared by the consecutive addition of hydrogen bromide and bromine to *dl*-carvone.[2]

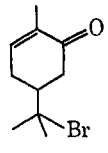
In the present study it was found expedient to isolate carvone hydrobromide (II) from the reaction of hydrogen bromide with carvone,[3] and then brominate hydrobromide II in acetic acid or methylene chloride to afford *dl*-I, mp 76°, or *d*-I, a liquid. If normal *trans*-diaxial addition to the double bond[4] and an equatorial bromoisopropyl group[5] are assumed, the conformation of I should be represented as Ia.



I



Ia



II

This conformational assignment was supported by spectral and chemical evidence. The nmr spectrum of I displayed an apparent triplet at 4.75 ppm assigned to the proton at C-3. The multiplicity of this signal and the spin–spin coupling constant sum of *ca.* 6 Hz was indicative of the X portion of an ABX system in which H_X bissects the angle between H_A and H_B.[6] The hydrogen at C-3 is therefore equatorial and the bromine is axial.

The singlet methyl resonance at 1.98 ppm attributed to the methyl group at C-2 was only shifted by *ca.* 1.8 Hz to higher field when the solvent was changed from deuteriochloroform to benzene. This is in accord with the presence of an equatorial methyl group, since axial α-methyl groups are normally shifted by *ca.* 12–20 Hz to higher field on passing from deuteriochloroform to benzene.[7]

The carbonyl stretching frequency of I showed a shift of 9 cm^{-1} from that of the parent ketone, carvomenthone.[8] This observation supports the axial assignment for the bromine at C-2, since an α-equatorial bromine usually produces a change of *ca.* 20 cm^{-1}.[9,10]

Additional evidence for an axial bromine at C-2 was provided by the ultraviolet spectrum of I, which shows a bathochromic shift of 21 mμ from that of carvomenthone and is accompanied by a substantial increase in intensity.[10,11]

Finally, it was observed that 93% of I was debrominated in 2 hr by sodium iodide in absolute methanol at 25°. Rapid elimination is in accord with the *trans*-diaxial assignment of the bromines at C-2 and C-3.[12]

A second carvone tribromide isomer, III, can be readily prepared from *d*-carvone by carrying out the bromine addition to carvone hydrobromide (II) in the presence of hydrogen bromide. This new isomer, III, mp 95–97°, was readily separated from the liquid isomer I by crystallization from pentane. Using *dl*-carvone, *dl*-carvone tribromide (III), mp 123–125°, was isolated in 44% yield. An nmr analysis of crude tribromide mixtures indicated that III and I were present in a ratio of 55:45.

The configuration of III was established with the aid of spectral and chemical evidence. The nmr spectrum of III exhibited a signal centered at 3.95 ppm attributed to the proton at C-3. The upfield position of the signal relative to that (4.75 ppm) of the proton at C-3 in tribromide I indicated the configuration of the hydrogen to be axial. In addition, the broad pair of doublets observed for this proton (J_{total} = 15 Hz) is indicative of the X portion of an ABX system in which H_X is axial and coupled with an axial and an equatorial proton.[6] Thus, the bromine at C-3 must be equatorial.

The chemical shift of the methyl group at C-2 is not altered appreciably by a change from deuteriochloroform to benzene. This suggest that the methyl is equatorial and the bromine is axial at C-2. The ultraviolet maximum at 306 mμ (ϵ 104) confirms the axial α-bromo assignment.

Tribromide III reacted slowly with sodium iodide in absolute methanol at 25°; after 2 hr, *ca.* 15% debromination to II had occurred whereas the debromination of

(1) (a) David Ross Research Fellow, Purdue University, 1967–1969; (b) 1964–1966.

(2) O. Wallach and C. Ohligmacher, *Ann.*, **305**, 245 (1899); O. Wallach, *ibid.*, **414**, 240 (1918).

(3) A. Baeyer, *Ber.*, **27**, 811 (1894).

(4) D. H. R. Barton and R. C. Cookson, *Quart. Rev.* (London), **10**, 44 (1956).

(5) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, pp 42–58, and references cited therein.

(6) N. Bhacca and D. Williams, "Applications of NMR Spectroscopy to Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 47–51 and 136–139.

(7) D. H. Williams and D. A. Wilson, *J. Chem. Soc., B*, 144 (1966); see also ref 6, pp 165–170.

(8) T. Lowry and R. Lishmund, *J. Chem. Soc.*, 709 (1935).

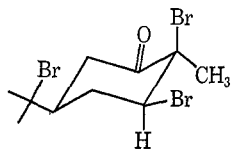
(9) R. Jones, D. Ramsey, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952).

(10) E. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 240–241.

(11) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(12) S. Winstein, D. Pressman, and W. G. Young, *J. Amer. Chem. Soc.*, **61**, 1645 (1939).

I was essentially complete in 2 hr. This observation agrees with the *cis* relationship of the vicinal bromine atoms in III.



III

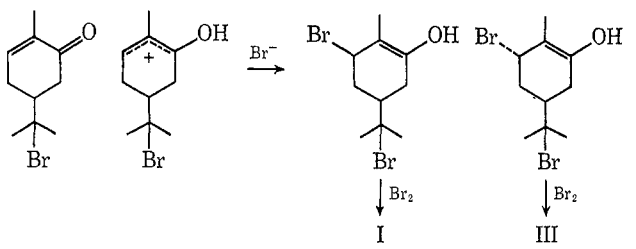
The structural assignment of III reached on the basis of spectral analysis (Table I) has been confirmed by three-dimensional X-ray analysis.[13]

TABLE I
SPECTRAL DATA FOR CARVONE TRIBROMIDES I AND III

			Nmr	
Compd	Ir C=O, cm^{-1}	Uv λ_{max}, $m\mu$ (ϵ)	CHBr, ppm	CH_3CBr Δ $CDCl_3$–C_6H_6
Carvomenthone	1717	286 (24)		
Tribromide I	1726	307 (130)	4.81	1.8
Tribromide III	1726	306 (104)	3.96	4.2

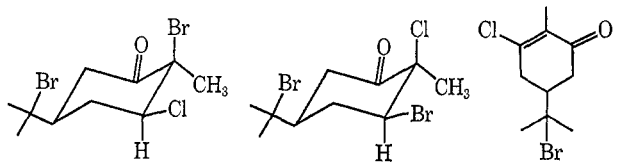
The formation of *cis*-tribromide III would appear to involve an overall *cis* addition of bromine to the conjugated double bond in II and could conceivably involve a Michael type of addition[14] of tribromide or bromide ions to the activated double bond, as pictured in Scheme I. Bromide or tribromide ion attack of

SCHEME I



cation A should occur with almost equal likelihood from either side of the cyclohexane ring and would account for the nearly identical quantities of *cis* and *trans* isomers isolated from the bromine addition. While this pathway may ultimately account for the formation of *cis*-tribromide III, the picture is complicated by the rapid formation of an equilibrium mixture of *ca.* 45% I and 55% III on brief (10–60 min) exposure of either pure I or III to hydrogen bromide in acetic acid at 0°. To explain this isomerization, an extensive study was undertaken.

On *prolonged* exposure to hydrogen chloride in acetic acid at 0°, *trans*-tribromide I gave two isomeric monochlorodibromocarvones, which were separated by careful fractional crystallization. The nmr spectrum of the higher melting isomer (mp 123–125°) was very similar to that of *cis*-tribromide III and displayed a signal at 3.68 ppm (J_{total} = 15 Hz) corresponding to an axial hydrogen at C-3. The difference in chemical shift of the α-methyl group in deuteriochloroform and benzene was only 3 Hz, indicating that the methyl at C-2 is equatorial. This latter assignment was supported by the appearance of an ultraviolet maximum at 304 $m\mu$ (ϵ 73) and carbonyl stretching frequency at 1721 cm^{-1} which dictated the presence of an axial α-halo substituent. Structures IV and V can be accommodated by this information.

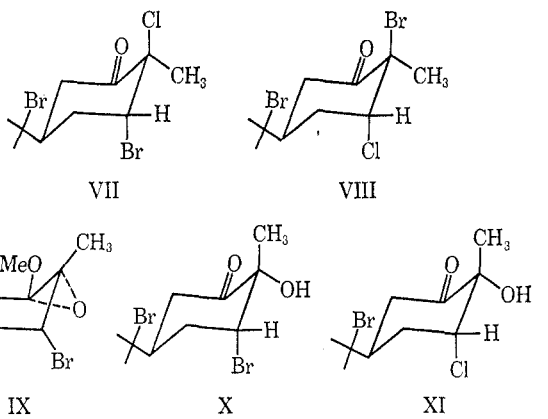


IV V VI

In order to differentiate between these two possibilities, the compound was dehydrohalogenated with isopropylamine in ether.[15] The product was shown to be the chloro bromo ketone VI and allows a choice of IV for one of the carvone chlorodibromides.

The second, lower melting chlorodibromide (mp 63–65°) displayed spectral characteristics almost identical with those of tribromide I. The appearance of a triplet signal at 4.75 ppm demonstrated that the proton at C-3 is equatorial, while the failure of benzene to induce a shift of the α-methyl resonance and ultraviolet absorption at 307 $m\mu$ (ϵ 79) placed the α-halo group axial and the methyl group equatorial.

In order to differentiate between the isomers VII and VIII, the lower melting isomer was allowed to react with sodium methoxide in ether. One of the products of the reaction of sodium methoxide in ether with tri-

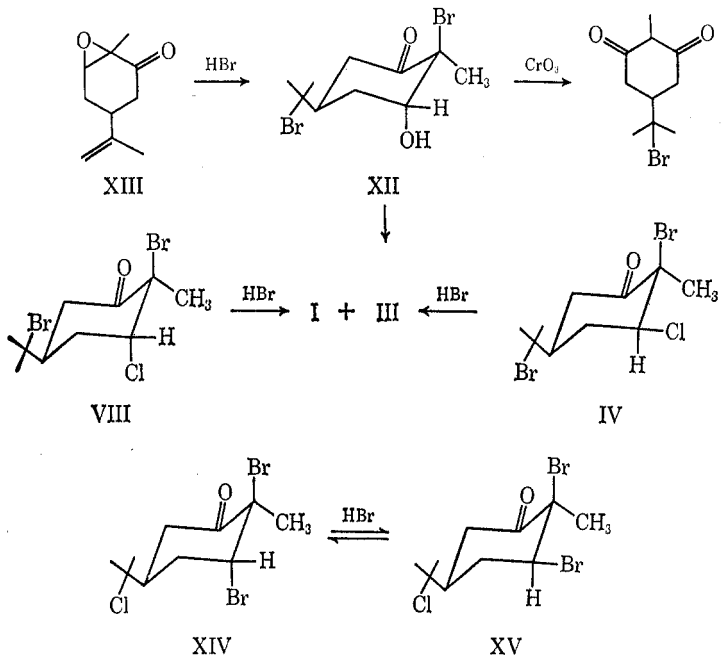


VII VIII

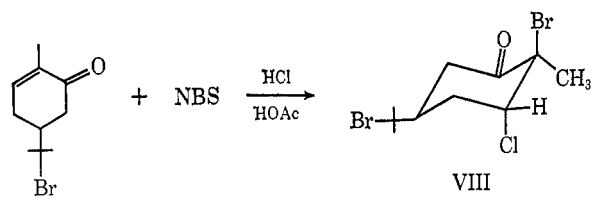
IX X XI

bromide I is the bromohydrin X, which is produced during the aqueous work-up of the reaction mixture by hydrolysis of epoxide IX.[16] By analogy, it was anticipated that VIII would give chlorohydrin XI, whereas VII would yield the known bromohydrin X. The product, mp 84–84.5°, actually obtained from this transformation was different from the bromohydrin X, mp 67–70°, and displayed fragment ions in its mass spectrum at *m/e* 159 and 161 (relative abundance *ca.* 3:1) corresponding to isotopic $C_7H_8O_2Cl^+$ species. Authentic X exhibited an analogous $C_7H_8O_2Br^+$ ion at *m/e* 203 and 205. The mass spectrum, along with infrared, nmr, and elemental analysis, indicates the product to be the chlorohydrin XI, allowing a choice of VIII as the lower melting chlorodibromide isomer. Additional evidence for this structural assignment was

(13) M. Rossman and R. W. Schevitz, American Crystallographic Association summer meeting, University of Minnesota, August 1967.
(14) P. B. D. de la Mare, *Quart. Rev.* (London), **3**, 138 (1949).
(15) J. Wolinsky and R. O. Hutchins, *J. Org. Chem.*, **33**, 407 (1968).
(16) J. Wolinsky and R. O. Hutchins, unpublished results.



obtained by an alternate synthesis of VIII *via dl*-carvone hydrobromide, N-bromosuccinimide, and hydrogen chloride.

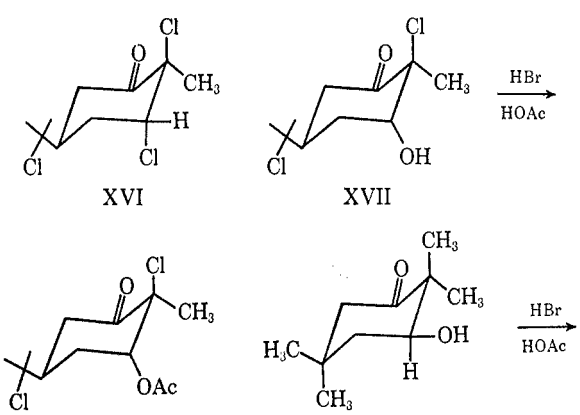


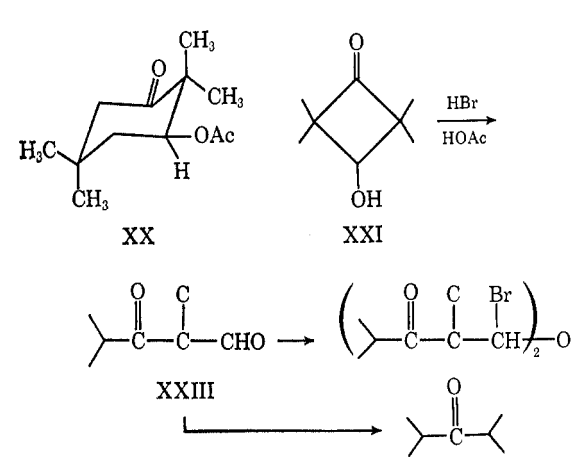
Exposure of either chlorodibromide IV or VIII, or bromohydrin XII, prepared by brief contact (1–2 min) of carvone oxide XIII with hydrogen bromide in acetic acid at 0°, to hydrogen bromide in acetic acid at 0° gave the equilibrium mixture of carvone tribromides I and III.

In each of these transformations, the 3 substituent (Br, Cl, OH) is cleanly replaced and no side process, other than a very slow conversion to phenolic material, is observed. The tertiary bromoisopropyl group is not affected under the reaction conditions, as it fails to exchange with chloride or acetate ions. Treatment of *trans*-carvone chlorodibromide (XIV) with hydrogen bromide in acetic acid at 0° gave an equilibrium mixture of *trans*-XIV and *cis*-carvone chlorodibromide (XV), providing further evidence for the lack of involvement of the tertiary haloisopropyl group.

Four other factors were found which contribute to the exchange of the 3 substituent. These include the presence of the carbonyl group, the presence of a bromine atom at C-2, the nature of the agent HX, and the configuration of the substituent at C-3.

The requirement of a bromine atom at C-2 is shown by the stability of *trans*-carvone trichloride (XVI) to the prolonged action of hydrogen chloride or bromide in acetic acid at 0–30°, and by the conversion of chlorohydrin XVII,[17] obtained by the action of hydrogen chloride on carvone oxide XIII, into an acetate derivative XVIII under conditions which smoothly transform bromohydrin XII into the mixture of carvone tribromides I and III.



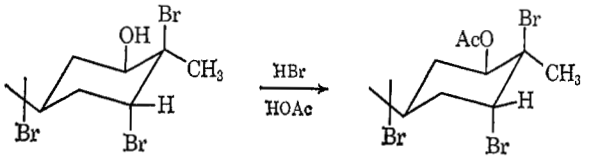


3-Hydroxy-2,2,5,5-tetramethylcyclohexanone (XIX) likewise gave an acetate XX under these conditions, while 3-hydroxy-2,2,4,4-tetramethylcyclobutanone (XXI) underwent retro aldol cleavage to give keto aldehyde XXII[18] and products derived thereof.

(17) The structure of the chlorohydrin was established by oxidation with "Jones reagent" to 2-chloro-5-(α-chloroisopropyl)-2-methyl-1,3-cyclohexanedione. Oxidation of bromohydrin XII gave 5-(2-bromoisopropyl)-2-methyl-1,3-cyclohexanedione and involves loss of the electropositive bromine at position 2.

(18) *Cf.* L. Dolby and C. Wilkins, *Tetrahedron Lett.*, 2379 (1964), for a related cleavage of a cyclobutane derivative.

The requirement of the carbonyl group for the isomerization was demonstrated as follows. Reduction of *trans*-carvone tribromide (I) with sodium borohydride afforded the tribromo alcohol XXIII, which was converted in high yield to an acetate derivative XXIV on standing with hydrogen bromide in acetic acid at 0°. There was no evidence for a change in the configuration of bromine atoms at C-2 or C-3.



XXIII XXIV

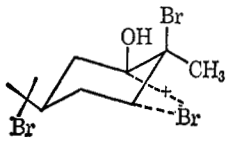
The transformations of *cis*- and *trans*-carvone tribromides (III and I) occur many times faster with hydrogen bromide (10–20 min) than with hydrogen chloride (the reaction with *trans*-I approaches completion after 116 hr at 0°; 15% reaction with *cis*-III occurs after 105 hr at 27°; no reaction is observed at 0° after 96 hr), and not at all with sodium bromide, sulfuric acid, perchloric acid, or trifluoroacetic acid under comparable or even somewhat more vigorous conditions. Furthermore, the reaction of *trans*-I with hydrogen chloride is not accelerated by the presence of perchloric acid.

Finally, the configuration and nature of the substituent at C-3 plays an important role in determining the rate of reaction. The rate of reaction of various substituents at C-3 with hydrogen bromide in acetic acid at 0° follow the order 3-axial bromine (<10 min) > 3-equatorial bromine ≅ 3-axial hydroxyl (*ca.* 10–20 min) ≫ 3-axial chlorine (1–3 hr) ⋙ 3-equatorial chlorine (*ca.* 23 hr).

An explanation for these changes must take into account the specific action of hydrohalides on an α-bromo carbonyl group resulting ultimately in the replacement of a substituent at the β carbon atom (C-3).

The exclusive exchange of substituents at the β position (C-3) and the failure of tribromo alcohol XXIII to undergo isomerization would seem to eliminate an isomerization mechanism which involves a diaxial–diequatorial conversion[19] followed by halide-catalyzed epimerization of the resulting equatorial α-bromo ketone to the more thermodynamically stable axial α-bromo ketone.[20]

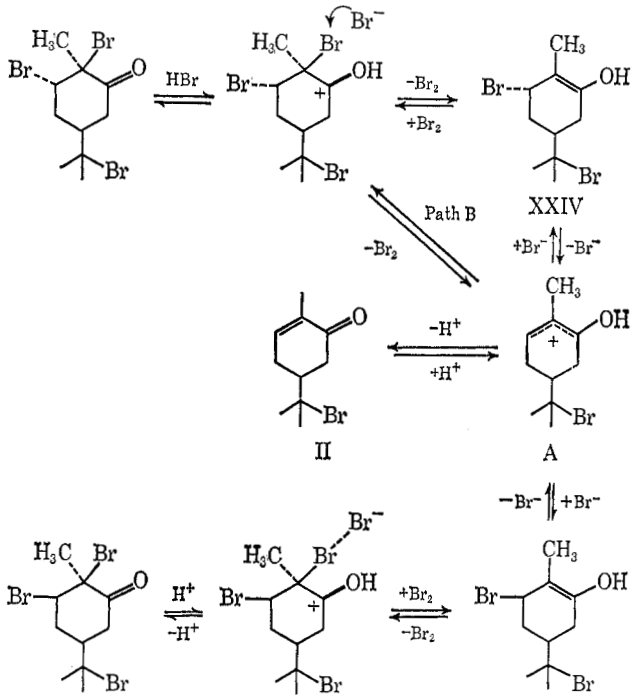
Also eliminated is the intervention of a bridged intermediate B, since it does not accommodate the specific requirement of an α bromine group or the facile isomerization of *cis*-carvone tribromide (III).



B

The elimination–addition mechanism depicted in Scheme II is consistent with all experimental observations. Protonation must play a role, since both *cis*- and *trans*-tribromides III and I are stable to sodium bromide in acetic acid. It is conceivable that debromination–bromination by sodium bromide might go undetected; however, this cannot be the case with *cis*-tribromide III, since debromination would afford carvone hydrobromide (II) which, in the absence of hydrogen bromide, would react with bromine to give *trans*-tribromide I.

SCHEME II



Protonation of the carbonyl group generates a cation adjacent to the α bromine atom. The electronic demand of the cation should increase the electropositive character of the α bromine atom and make it more vulnerable to attack by a reducing agent such as bromide or chloride ion.[19] The faster rate of isomerization by hydrogen bromide and the stability of α-chlorocarvone derivatives toward hydrohalides strongly implicate halide attack on the α bromine atom.[21]

The slower isomerization of the *cis*-carvone trihalide isomers (3-halo equatorial) may be a consequence of a stepwise mechanism involving the formation of enol XXIV followed by slow ionization of the 3-halo substituent to produce ion A, which is most likely in equilibrium with carvone hydrobromide (II). The faster rate of the *trans* isomers (3-halo axial) may be accounted for by a concerted process[22] (path B). A rapid stepwise ionization of the axial C-3 bromine atom accelerated by σ overlap with the π orbitals of the allylic cation[23] can be rejected in view of the fact that 3β-chlorocholest-4-ene (quasi-equatorial) and 3α-chlorocholest-4-ene (quasi-axial) solvolyze in ethanol–dioxane

(19) D. H. R. Barton and E. Miller, *J. Amer. Chem. Soc.*, **72**, 1066 (1950); D. H. R. Barton, E. Miller, and H. Young, *J. Chem. Soc.*, 2598 (1951); C. Grob and S. Winstein, *Helv. Chim. Acta*, **35**, 782 (1952); G. Alt and D. H. R. Barton, *J. Chem. Soc.*, 4284 (1954); D. H. R. Barton and J. King, *ibid.*, 4398 (1958).

(20) E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 2301, 3297, 4382 (1953); C. Djerassi, N. Finch, R. C. Cookson, and C. Bird, *ibid.*, **82**, 5488 (1960); E. R. H. Jones and D. Wiluka, *J. Chem. Soc.*, 911 (1959); J. Fajkos, *ibid.*, 3966 (1959).

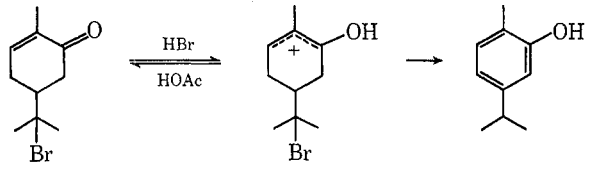
(21) *Cf.* B. Ellis and V. Petrow, *J. Chem. Soc.*, 3869 (1953); J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954); H. L. Goering and H. H. Espy, *J. Amer. Chem. Soc.*, **77**, 5023 (1955); B. Miller, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. Griffith, Ed., Interscience Publishers, New York, N. Y., 1965, p 133.

(22) J. Hine and W. H. Buder, *J. Amer. Chem. Soc.*, **77**, 361 (1955); S. J. Cristol, J. Q. Weber, and M. C. Brindell, *ibid.*, **78**, 598 (1956).

(23) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

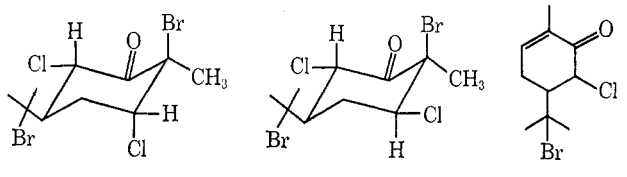
at almost identical rates; the 3α (quasi-axial) isomer actually solvolyses somewhat more slowly than the 3β (quasi-equatorial) isomer.[24]

An attempt to demonstrate the intermediacy of carvone hydrobromide (II) by nmr spectroscopy proved fruitless, since it was independently established that carvone hydrobromide II is completely protonated under the conditions of the isomerization. This was suggested by the fact that the olefinic proton of I could not be detected (probably covered by the OH resonance of the solvent) when its nmr spectrum was determined in acetic acid saturated with hydrogen bromide, nor was a signal for -CHBr or CH_3CH- observed. Carvone hydrobromide II was recovered after short treatment with hydrogen bromide in acetic acid, but after the solution had stood for more than 24 hr, an appreciable amount of carvacrol (nmr and isolation) was produced.



A

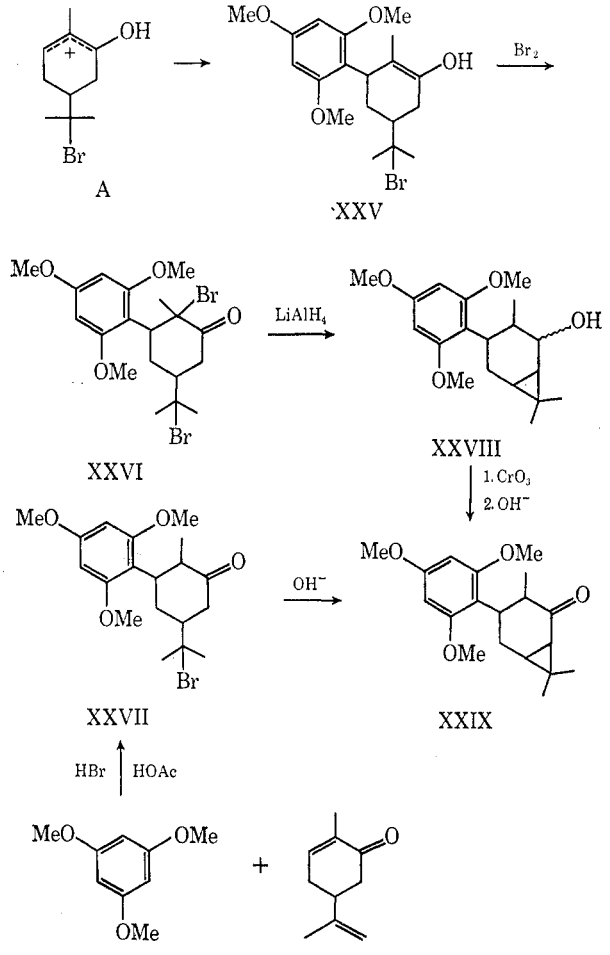
An attempt to trap carvone hydrobromide II by conducting the isomerization wih hydrogen chloride in the presence of chlorine resulted in the production of a complicated mixture of products, from which the following were isolated and characterized by their spectral properties.



Attempts were also made to trap the bromine produced in the debromination step. When phloroglucinol was added with carvone tribromide I to hydrogen bromide in acetic acid, there was obtained an unidentified, intractable product. When 1,3,5-trimethoxybenzene was used in place of phloroglucinol, a crystalline solid was isolated which was formulated as XXVI on the basis of spectral and chemical evidence. Thus, 1,3,5-trimethoxybenzene failed to trap bromine and instead trapped ion A.

The formation of XXVI can be accounted for by assuming that ion A alkylates the activated benzene ring and that bromination of the resulting enol XXV occurs faster than substitution of the aromatic ring. This notion is supported by the facile formation of XXVII by the reaction of *dl*-carvone with 1,3,5-trimethoxybenzene catalyzed by hydrogen bromide in acetic acid. Reduction of XXVI with lithium aluminum hydride to XXVIII followed by oxidation and equilibration of the 2-methyl group with base gave carone XXIX, which was identical with the product obtained in the reaction of XXVII with base.

(24) W. E. Young, R. E. Ireland, T. I. Wrigley, C. W. Shoppee, B. D. Agashe, and G. H. R. Summers, *J. Amer. Chem. Soc.*, **81**, 1452 (1959).



Bromine was finally trapped by carrying out the equilibration in the presence of sulfur dioxide. The major component of the complicated mixture which resulted was carvone hydrobromide II. It was independently established that carvone tribromide I is stable to sulfur dioxide.

Experimental Section[25]

Preparation of 2-Methyl-5-(2-bromoisopropyl)cyclohexenone (Carvone Hydrobromide II).—A solution of 40.0 g (0.266 mol) of *dl*-carvone in 40 ml of acetic acid was added to 100 ml of cold acetic acid saturated with dry HBr. The resulting solution was stirred at 0° for 30 min and poured into ice–water. The water mixture was extracted three times with ether, and the ether layer was washed well with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 57.4 g (94%) of light red oil which solidified upon cooling. Recrystallization from hexane gave 55.7 g of *dl*-carvone hydrobromide: mp 37–39° (lit.[3] mp 37°); ir (melt) 5.98 μ (C=C–C=O); nmr (CCl_4) δ 1.72 (s, 3, CH_3C=C), 1.79 [s, 6, $(CH_3)_2CBr$], 2.12–2.83 (m, 5), and 6.70 (m, 1, CH=C–C=O).

d-Carvone hydrobromide was prepared in an identical manner and showed mp 31–32° (lit.[3] mp 30–32°) and spectral properties identical with those of the racemic mixture.

Preparation of 2a,3a-Dibromo-2-methyl-5-(2-bromoisopropyl)-cyclohexanone (*trans*-Carvone Tribromide I).—To a solution of 40.0 g (0.173 mol) of *dl*-carvone hydrobromide in 100 ml of acetic acid was added, dropwise over a 90-min period with stirring and cooling, 27.7 g (0.173 mol) of bromine in 25 ml of acetic acid. The solution was allowed to stir at 0° for 2 hr and was poured

(25) All melting points are uncorrected. Infrared spectra were determined with Perkin-Elmer Model 221 and Infracord spectrometers. Nmr spectra were measured at 60 MHz with a Varian Associates A-60 spectrometer. Ultraviolet spectra were determined with a Bausch and Lomb 505 spectrophotometer. Mass spectra were measured with a Hitachi RMU-6D mass spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

into ice–water. The water mixture was extracted with ether, and the ether layer was washed well with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 64.4 g (94%) of light yellow oil which solidified upon standing. Recrystallization from hexane gave 63.2 g of *dl-trans*-carvone tribromide, mp 73–75° (lit.[2] mp 74–76°); ir (Nujol) 5.80 μ (C=O); ir ($CHCl_3$) 1726 cm^{-1}; uv λ_{max} 307 mμ (ϵ 130); nmr ($CDCl_3$) δ 1.77, 1.80 [2 s, 6, $(CH_3)_2CBr$], 1.98 (s, 3, CH_3CBr), 2.10–3.60 (m, 5), and 4.81 (t, 1, J = 3 Hz, equatorial HCBr).

The addition of bromine to *d*-carvone hydrobromide gave an oil, which solidified on cooling to −20° and melted on warming to 0°. Thin layer chromatography indicated the oil to be pure *d-trans*-carvone tribromide.

Preparation of 2a,3e-Dibromo-2-methyl-5-(2-bromoisopropyl)-cyclohexanone (*dl-cis*-Carvone Tribromide III).—To a solution of 10.0 g (0.067 mol) of *dl*-carvone in 50 ml of acetic acid was added, dropwise with stirring and cooling, 40 ml of cold acetic acid saturated with dry HBr. The solution was allowed to stir at 0° for 1 hr, and then 10.7 g (0.067 mol) of bromine in 25 ml of acetic acid was added dropwise. The dark solution was allowed to stir at 0° for 2 hr, and was then poured into ice–water. The water mixture was extracted with ether, and the ether layer was washed with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 24.2 g (92%) of light brown oil. The oil was dissolved in hot hexane and cooled to 0° to give 10.4 g (40%) of *dl-cis*-carvone tribromide: mp 124–125°; ir (Nujol) 5.80 μ (C=O); uv λ_{max} 306 mμ (ϵ 104); nmr ($CDCl_3$) δ 1.78, 1.82 [2 s, 6, $(CH_3)_2CBr$], 1.95 (s, 3, CH_3CBr), 2.20–3.70 (m, 5), 3.96 (2 d, 1, J = 15 Hz, axial HCBr).

Anal. Calcd for $C_{10}H_{15}Br_3O$: C, 30.72; H, 3.86; Br, 61.31. Found: C, 30.47; H, 4.03; Br, 61.00.

The filtrate from above was concentrated and cooled to −20° to give 12.4 g (47.5%) of white crystals which proved to be identical with *dl-trans*-carvone tribromide.

The addition of hydrogen bromide and bromine to *d*-carvone using the same conditions afforded *d-cis*-carvone tribromide (III), mp 94.5–96°, whose spectral properties were identical with those of the racemic mixture III.

Debromination of *trans*- and *cis*-Carvone Tribromides.—A solution of 384.9 mg (2.56 mmol) of sodium iodide and 200.8 mg (0.513 mmol) of *trans*-carvone tribromide (I) in 50 ml of absolute methanol was stirred at 25° for 2 hr, during which time the color of the solution gradually turned to very deep red-black. *Ca.* 30 ml of water was added and the solution was titrated with 0.1 *N* sodium thiosulfate solution to indicate that 93% debromination had taken place.

In a separate experiment, the product from debromination was isolated by dilution with water and extraction with ether. The infrared spectrum of the resulting oil was identical with that of carvone hydrobromide (II) except for an OH peak at 3.0 μ. The nmr spectrum (CCl_4) of a sublimed sample showed equal amounts of II and carvacrol.

Using the same conditions, the solution from *cis*-tribromide III had turned a pale orange color in 2 hr and titration indicated 15% debromination had occurred. The resulting solution was diluted with water and extracted with ether. The ether solution was dried over $MgSO_4$ and concentrated to leave 176.6 mg of crystalline residue. Recrystallization from *n*-hexane gave pure *d-cis*-tribromide III, mp 94–95°.

Isomerization of *cis*- and *trans*-Carvone Tribromides III and I with Hydrogen Bromide.—To a solution of 3.0 g (0.0077 mol) of *trans*-carvone tribromide I in 35 ml of acetic acid was added 40 ml of cold acetic acid saturated with dry HBr. The resulting light yellow solution was allowed to stand at 0° for 1 hr, poured into ice–water, and extracted with ether. The ether was washed with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 2.85 g of white solid. The solid mixture was analyzed by nmr spectroscopy and was found to contain 44% *trans*-carvone tribromide and 56% *cis*-carvone tribromide by measuring the peak heights of the 2-methyl signals. That this method of analysis was accurate was shown by fractional crystallization of the crude mixture from hexane, yielding (1) 1.40 g of white needles, mp 199–121°, whose ir and nmr spectra were identical with those of *cis*-carvone tribromide III; and (2) 1.16 g of plates, mp 74–76°, whose ir and nmr spectra were identical with those of *trans*-carvone tribromide.

When pure *cis*-carvone tribromide (III) was employed instead of *trans*-I, an identical mixture of I and III resulted.

Reaction of *trans*-Carvone Tribromide with Hydrogen Chloride. Preparation of 3a- and 3e-Chloro-2a-bromo-2-methyl-5-(2-bromoisopropyl)cyclohexanone.—To a solution of 11.0 g (0.026 mol) of *trans*-carvone tribromide (I) in 15 ml of acetic acid was added 100 ml of cold acetic acid saturated with dry HCl. The resulting solution was allowed to stand at 0° for 39 hr, poured into ice–water, and extracted with ether. The ether was washed with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give a light brown oil which solidified upon standing. The solid material was dissolved in hot hexane and cooled to 0° to give 2.50 g (28%) of 2a-bromo-2-methyl-3e-chloro-5-(2-bromoisopropyl)cyclohexanone (IV): mp 121–123°; ir (Nujol) 5.80 μ (C=O); ir ($CHCl_3$) 1721 cm^{-1}; uv λ_{max} 304 mμ (ϵ 73); nmr ($CDCl_3$) δ 1.75, 1.80 [2, s, 6, $(CH_3)_2$-CBr], 1.91 (s, 3, CH_3CBr), 2.40–3.60 (m, 5), and 3.82 and 3.90 (2 d, 1, J = 15 Hz, axial HCCl).

Anal. Calcd for $C_{10}H_{15}Br_2ClO$: C, 34.66; H, 4.39; Cl, 10.23; Br, 46.12. Found: C, 34.43; H, 4.40; Cl, 10.47; Br, 46.40.

Cooling the filtrate to −20° gave 4.80 g of additional material, which by nmr analysis proved to be a mixture of the 3a-chloro and 3a-bromo isomers. This mixture was further treated with HCl in acetic acid for 46 hr. After work-up as above, 300 mg of the 3e-chloro compound IV was obtained along with 1.80 g of 2a-bromo-2-methyl-3a-chloro-5-(2-bromoisopropyl)cyclohexanone (VIII): mp 62–64°; ir (Nujol) 5.80 μ (C=O); uv λ_{max} 307 mμ (ϵ 79); nmr ($CDCl_3$) δ 1.74, 1.80 [2 s, 6, $(CH_3)_2CBr$], 1.92 (s, 3, CH_3CBr), 2.20–3.60 (m, 5), and 4.70 (t, 1, J = 3 Hz, equatorial HCCl).

Anal. Calcd for $C_{10}H_{15}Br_2ClO$: C, 34.66; H, 4.39; Br, 46.12; Cl, 10.23. Found: C, 34.38; H, 4.67; Br, 45.90; Cl, 9.98.

Dehydrobromination of Dibromochlorocarvone IV.—A solution of 50 mg (0.045 mmol) of dibromochlorocarvone IV and 160 mg (2.72 mmol) of isopropylamine in 15 ml of anhydrous ether was stirred at room temperature for 12 hr. The precipitated salts were removed, the ether was evaporated, and the residue was evaporatively distilled to give 40 mg of a colorless oil: ir 5.98 and 6.12 μ (O=C–C=C); nmr (CCl_4) δ 1.80 [s, 6, $(CH_3)_2$-CBr], 1.89 (t, 3, J = 1.5 Hz, $CH_3C{=}CCH_2$), and 2.0–3.0 (complex multiplets).

The 2,4-dinitrophenylhydrazine derivative of this oil was obtained as bright orange needles, mp 171–173°, after several recrystallizations from ethyl acetate–ethanol.

Anal. Calcd for $C_{16}H_{18}BrClN_4O_4$: C, 43.12; H, 4.07; Br, 17.93; Cl, 7.95. Found: C, 43.03; H, 3.90; Br, 18.00; Cl, 7.70.

Preparation of 2a-Bromo-2-methyl-3a-chloro-5-(2-bromoisopropyl)cyclohexanone (VIII).—To a solution of 10.0 g (0.043 mol) of *dl*-carvone hydrobromide (II) in 100 ml of cold acetic acid saturated with dry hydrogen chloride was added 7.70 g (0.043 mol) of N-bromosuccinimide. The resulting solution was stirred at 10–20° for 2 hr and worked up in the usual manner to give 11.9 g (80%) of light brown solid. The material was recrystallized from hexane to give 11.5 g of chlorodibromide VIII, mp 64–65°. The ir, nmr and mass spectra of this material were identical with those of the *trans*-chlorodibromide formed in the reaction of I with HCl.

Reaction of Chlorodibromide VIII with Sodium Methoxide in Diethyl Ether.—To a solution of 3.0 g (8.7 mmol) of chlorodibromide VIII in 75 ml of dry ether was added 3.0 g (0.056 mol) of sodium methoxide. The mixture was stirred at room temperature for 20 hr, 10 ml of water was added, and the mixture was stirred for 15 min. The water layer was extracted with ether and the combined ether layers were dried ($MgSO_4$), concentrated, and cooled to give 560 mg of white crystalline solid. The solid was recrystallized from hexane to give 2e-hydroxy-2-methyl-3a-chloro-5-(2-bromoisopropyl)cyclohexanone (XI): mp 84–84.5°; ir (Nujol) 2.85 (OH) and 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.51 (s, 3, CH_3), 1.77, 1.80 [2 s, 6, $C(CH_3)_2$], 2.20–2.90 (m, 5), 3.80 (s, 1, OH), and 4.50 (t, 1, J = 3 Hz, equatorial HC).

Anal. Calcd for $C_{10}H_{16}BrClO_2$: C, 42.34; H, 5.64; Br, 28.19; Cl, 12.50. Found: C, 42.23; H, 5.75; Br, 27.92; Cl, 12.27.

Preparation of *d,l*-Carvone Hydrochloride.—A solution of 100 ml of cold acetic acid saturated with dry HCl was added dropwise with cooling and stirring to a solution of 25.0 g (0.167 mol) of *dl*-carvone in 20 ml of cold acetic acid. After the addition was complete, the solution was allowed to stir at room temperature for 3 hr and then worked up in the usual manner to give 25.6 g (83.4%) of *dl*-carvone hydrochloride. The light yellow liquid was of sufficient purity to be used in subsequent reactions.

Preparation of 2a,3a-Dibromo-2-methyl-5-(2-chloroisopropyl)-cyclohexanone (XIV).—To a solution of 15.0 g (0.081 mol) of

carvone hydrochloride in 50 ml of acetic acid was added dropwise with stirring and cooling 13.0 g (0.082 mol) of bromine in 25 ml of acetic acid. After the addition was complete, the solution was allowed to stir at 10–15° for 2 hr and poured into ice–water. The usual work-up gave a light brown oil which was dissolved in hexane and cooled to give 20.67 g (74%) of chlorodibromide ketone XIV: mp 55–57°; ir (Nujol) 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.60 [s, 6, $(CH_3)_2CCl$], 2.0 (s, 3, CH_3CBr), 2.20–3.40 (m, 5), and 4.83 (t, 1, J = 3 Hz, equatorial HCBr).

Reaction of 2a,3a-Dibromo-2-methyl-5-(2-chloroisopropyl)cyclohexanone (XIV) with Hydrogen Bromide.—To a solution of 3.0 g (0.009 mol) of chloro *trans*-dibromo ketone XIV in 15 ml of acetic acid was added 40 ml of cold acetic acid saturated with dry HBr. The resulting solution was allowed to stand at 0° for 16 hr, and poured into ice–water. The usual work-up gave a light yellow oil which was dissolved in hot hexane and cooled to 0° to give 1.47 g (49%) of chloro *cis*-dibromo ketone XV: mp 110–112°; ir (Nujol) 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.55, 1.58 [2 s, 6, $(CH_3)_2CCl$], 1.90 (s, 3, CH_3CBr), 2.30–3.40 (m, 5), and 3.81 and 3.91 (2 d, 1, J = 9 Hz, axial HCBr).

The filtrate was concentrated and cooled to −20° to give 1.31 g (44%) of white crystals, mp 56–58°. The spectral data showed this compound to be starting material (XIV).

Preparation of 2a,3a-Dichloro-2-methyl-5-(2-chloroisopropyl)-cyclohexanone (*trans*-Carvone Trichloride, XVI).—To a solution of 5.0 g (0.042 mol) of carvone hydrochloride in 20 ml of acetic acid was added, dropwise with stirring and cooling, 3.0 g (0.042 mol) of chlorine dissolved in 100 ml of acetic acid. After the addition was complete, the solution was allowed to stir at 10–15° for 2 hr and poured into ice–water. The usual work-up gave a light yellow oil which was dissolved in hexane and cooled to give 4.93 g (46%) of *trans*-carvone trichloride (XVI): mp 33–35°; ir (Nujol) 5.75 μ (C=O); nmr ($CDCl_3$) δ 1.58, 1.60 [2 s, 6, $(CH_3)_2CCl$], 1.75 (s, 3, CH_3CCl), 2.10–3.20 (m, 5) and 4.58 (t, 1, J = 3 Hz, equatorial HCCl).

Preparation of Carvone Epoxide.—To a cold solution of 15.0 g (0.10 mol) of *dl*-carvone and 29.0 ml (0.30 mol) of 30% hydrogen peroxide in 100 ml of methanol was added dropwise, over a 60-min period, 8.3 ml (0.05 mol) of 6 *N* sodium hydroxide. The mixture was stirred at 20–30° for 3.5 hr and poured into 200 ml of cold water. The mixture was extracted with ether, and the ether was washed with water, dried ($MgSO_4$), and concentrated to give a colorless oil. Distillation of the oil *in vacuo* gave 10.13 g (61%) of carvone epoxide: bp 83–85° (0.8 mm); $n^{20}D$ 1.4818 [lit.[26] bp 120–122° (15 mm); $n^{20}D$ 1.4812].

Reaction of Carvone Epoxide with Hydrogen Chloride.—To a solution of 3.0 g (0.018 mol) of carvone epoxide in 5.0 ml of acetic acid was added 20 ml of cold acetic acid saturated with dry HCl. The resulting solution was allowed to stand at 0° for 39 hr an worked up in the usual manner to give a light brown oil, which was dissolved in hot hexane and cooled to give 2.36 g (55%) of 2a-chloro-2-methyl-3a-hydroxy-5-(2-chloroisopropyl)-cyclohexanone (XVII): mp 78–79°; ir (Nujol) 2.85 (OH) and 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.58 [s, 6, $(CH_3)_2CCl$], 1.63 (s, 3, CH_3CCl), 2.00–3.30 (m, 5), and 4.26 (broad s, 1, HCOH).

Anal. Calcd for $C_{10}H_{16}Cl_2O_2$: C, 50.21; H, 6.69; Cl, 29.71. Found: C, 50.06; H, 6.41; Cl, 29.58.

Oxidation of 2a-Chloro-2-methyl-3a-hydroxy-5-(2-chloroisopropyl)cyclohexanone (XVII).—To a solution of 400 mg (1.7 mmol) of keto chlorohydrin XVII in 10 ml of acetone was added 1 ml of freshly prepared Jones reagent.[27] The resulting mixture was stirred for 1 hr at room temperature and was worked up to give 390 mg (98%) of 2-chloro-2-methyl-5-(2-chloroisopropyl)-cyclohexane-1,3-dione: mp 68–69°; ir (Nujol) 5.75 and 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.62 (s, 9, CH_3CCl), and 2.50–3.70 (m, 5).

Anal. Calcd for $C_{10}H_{14}Cl_2O_2$: C, 50.63; H, 5.91; Cl, 29.96. Found: C, 50.59; H, 6.12; Cl, 29.84.

Reaction of 2a-Chloro-2-methyl-3a-hydroxy-5-(2-chloroisopropyl)cyclohexanone (XVII) with Hydrogen Bromide.—A cold solution of 25 ml of acetic acid saturated with dry HBr was added to 300 mg (1.3 mmol) of keto chlorohydrin XVII in 5 ml of acetic acid. The resulting solution was allowed to stand at 0° for 52 hr, and then worked up to give 250 mg of 2a-chloro-2-methyl-3a-acetoxy-5-(2-chloroisopropyl)cyclohexanone. Vpc collection of a small portion of the oil gave a clear liquid: ir (neat) 5.70, 5.80 (C=O), and 8.0 μ (OAc); nmr ($CDCl_3$) δ 1.52 (s, 3, CH_3CCl), 1.57 [s, 6, $(CH_3)_2CCl$], 2.03 (s, 3, CH_3CO_2), 2.20–3.20 (m, 5), and 5.40 (t, 1, J = 3 Hz, equatorial HCOAc).

Preparation of 2a-Bromo-2-methyl-3a-hydroxy-5-(2-bromoisopropyl)cyclohexanone (XII).—A mixture of 5.0 g (0.03 mol) of carvone epoxide, 50 ml of 48% hydrobromic acid, and 40 ml of chloroform was stirred at room temperature for 1 hr. The chloroform layer was drawn off, washed with water and 5% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give a purple solid. The solid material was dissolved in ether–hexane, treated with Norit, filtered, and cooled to give 4.35 g (44%) of keto bromohydrin XII: mp 95–96°; ir (Nujol) 2.90 (OH) and 5.80 μ (C=O); uv λ_{max}^{EtOH} 307 mμ (ε 95); nmr ($CDCl_3$) δ 1.78, 1.80 [2 s, 6, $(CH_3)_2CBr$], 1.84 (s, 3, CH_3CBr), 2.30–3.40 (m, 5), and 4.40 (t, 1, J = 3 Hz, equatorial HCOH).

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.97; Br, 48.72. Found: C, 36.90; H, 4.97; Br, 48.45.

A mixture of 390 mg of the keto bromohydrin XII, 10 ml of acetyl chloride, and *ca.* 1.0 g of powdered magnesium was stirred at room temperature for 26 hr, poured into aqueous sodium bicarbonate solution, and extracted with ether. The ether solution was dried and evaporated. The resulting oil was dissolved in hexane, treated with charcoal, and cooled to −20°, affording crystals which after several recrystallizations from *n*-hexane gave colorless needles: mp 47–50°; ir (Nujol) 5.72, 5.80 (C=O), and 8.00 μ (OAc); uv λ_{max}^{EtOH} 306 mμ (ε 153); nmr ($CDCl_3$) δ 1.75, 1.77 [2 s, 9, $(CH_3)_2CBr$), CH_3CBr], 2.04 (s, 3, CH_3C=O), 1.5–3.5 (m, 5), and 5.51 (t, 1, J = 3 Hz, equatorial HCOAc).

Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.95; H, 4.89; Br, 43.19. Found: C, 39.04; H, 5.10; Br, 43.52.

Oxidation of 2a-Bromo-2-methyl-3a-hydroxy-5-(2-bromoisopropyl)cyclohexanone (XII).—To a solution of 1.0 g (0.003 mol) of keto bromohydrin XII in 20 ml of acetone was added 2.0 ml of freshly prepared Jones reagent[26] with control of the temperature below 25°. The mixture was stirred at room temperature for 1 hr and worked up in the usual manner to give 300 mg of light brown solid. Recrystallization from hexane gave 210 mg (22%) of 2-methyl-5-(2-bromoisopropyl)cyclohexane-1,3-dione: mp 120–122°; ir (Nujol) 3.0–3.7 (C=COH) and 6.3 (C=CO); nmr (pyridine) δ 1.13 [s, 6, $(CH_3)_2CBr$], 1.50 (s, 3, O=CCCH$_3$), and 1.60–2.20 (m, 5); mass spectrum m/e 246 and 248 (parent ions, ratio 1:1.

Reaction of 2a-Bromo-2-methyl-3a-hydroxy-5-(2-bromoisopropyl)cyclohexanone (XII) with Hydrogen Bromide.—To a solution of 3.0 g of keto bromohydrin XII in 25 ml of acetic acid was added 35 ml of cold acetic acid saturated with dry HBr. The resulting solution was allowed to stand at 0° for 44 hr and worked up to give a light brown oil, which was dissolved in hexane and cooled to 0° to give 1.6 g (45%) of white solid, mp 122–124°, whose infrared and nmr spectra were identical with those of *cis*-carvone tribromide (III).

The filtrate was further cooled to −20° to give 1.6 g (45%) of light brown solid, mp 71–74°, whose infrared and nmr spectra were identical wth those of *trans*-carvone tribromide (I).

Sodium Borohydride Reduction of *trans*-Carvone Tribromide (I). Preparation of Tribromo Alcohol XXIII.—To a solution of 1.0 g (3.35 mmol) of *dl*-carvone tribromide I in 60 ml of ether was added a solution of 0.572 g (15.1 mmol) of sodium borohydride in 45 ml of methanol. The solution was stirred at room temperature for 1.5 hr and 100 ml of pentane was added. The solution was washed with water, dried ($MgSO_4$), and concentrated to give 933 mg of pale yellow oil which solidfied upon standing. Recrystallization from hexane–carbon tetrachloride afforded white crystals: mp 87–88°; ir ($CHCl_3$) 2.75 μ (OH); nmr ($CDCl_3$) δ 1.79 [s, 6, $(CH_3)_2CBr$], 2.07 (s, 3, CH_3CBr), 1.90–2.90 (m, 5), 3.64 (q, 1, J = 14 Hz, axial HCOH), and 4.85 (t, 1, J = 3 Hz, equatorial HCBr).

Anal. Calcd for $C_{10}H_{17}Br_3O$: C, 30.56; H, 4.36; Br, 61.00. Found: C, 30.46; H, 4.45; Br, 61.18.

A solution of 400 mg of tribromo alcohol XXIII in 10 ml of acetyl chloride was stirred with 700 mg of powdered magnesium at room temperature for 37 hr and slowly poured into ice–water. The water mixture was extracted with ether, and the ether was washed with 10% sodium bicarbonate solution, dried ($MgSO_4$), and concentrated to give 432 mg of an oil, which was crystallized from pentane to give 360 mg of acetate XXIV: mp 99–101°; ir ($CHCl_3$) 5.80 μ (C=O); nmr ($CDCl_3$) δ 1.78 [s, 6, $(CH_3)_2CBr$], 1.93 (s, 3, CH_3CBr), 2.12 (s, 3, CH_3CO), 2.20–2.80 (m, 5), 4.76 (t, 1, J = 3 Hz, equatorial HCBr), and 5.05 (q, 1, J_{total} = 14.5 Hz, axial HCOAc).

(26) W. Treibs, *Ber.*, **65**, 1314 (1932).

(27) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

Anal. Calcd for $C_{12}H_{19}Br_3O$: C, 33.13; H, 4.40; Br, 55.11. Found: C, 33.40; H, 4.62; Br, 54.77.

Attempted Isomerization of Tribromo Alcohol XXIII with Hydrogen Bromide.—A solution of 100 mg of tribromo alcohol XXIII in 2 ml of acetic acid saturated with dry HBr was allowed to stand at 0° for 48 hr and poured into ice–water. The water mixture was extracted with ether, and the ether was washed with 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give a white solid, which was recrystallized from hexane to give acetate XXIV, mp 98–100°, whose ir and nmr spectra were identical with those of the acetate XXIV prepared above.

Attempted Trapping of the Enol Intermediate XXIV by the Addition of Chlorine.—To a solution of 5.0 g (0.013 mol) of *trans*-carvone tribromide (I) in 40 ml of acetic acid was added 50 ml of cold acetic acid saturated with dry HCl. To this solution was added 75 ml of cold acetic acid saturated with chlorine. The resulting light green solution was allowed to stand at 0° for 87 hr and worked up as usual to give a light yellow oil. Fractional crystallization from hexane gave two fractions. The ir spectrum of fraction A showed a carbonyl shift of *ca.* 20 cm^{-1} so a higher frequency from tribromide I, indicating the presence of an equatorial α-halo ketone. The nmr spectrum of fraction A was similar to the mixture of *cis*- and *trans*-chlorodibromides IV and VIII formed in the reaction of *trans*-tribromide I with HCl, with the exception of a doublet at δ 5.42 (J = 8.5 Hz) which supports the presence of an equatorial α-halo ketone. The spectral data suggests fraction A to be a mixture of 3e,6e-dichloro-2a-bromo-2-methyl-5-(2-bromoisopropyl)cyclohexanone and 3a,6e-dichloro-2a-bromo-2-methyl-5-(2-bromoisopropyl)cyclohexanone. Preparative thin layer chromatography on fraction B gave a small amount of solid material, whose nmr spectrum ($CDCl_3$) showed signals at δ 1.80 (s, 9, CH_3), 2.7–2.9 (m, 3), 4.64 (d, 1, J = 3 Hz, equatorial HCCl), and 6.67 (broad s, 1, CH=CO). The data suggest the compound to be 6a-chloro-2-methyl-5-(2-bromoisopropyl)-2-cyclohexenone.

Reaction of *trans*-Carvone Tribromide (I) with Hydrogen Bromide in the Presence of Trimethoxybenzene.—To a solution of 5.0 g (0.013 mol) of *trans*-carvone tribromide (I) and 2.18 g (0.013 mol) of trimethoxybenzene in 30 ml of acetic acid was added 40 ml of cold acetic acid saturated with dry HBr. The resulting solution was allowed to stand at 0° for 8 hr and worked up to give a light brown oil. The oil was dissolved in hot hexane and cooled to 0° to give 350 mg of white crystals, mp 123–124°, whose infrared and mmr spectra were identical with those of *cis*-carvone tribromide. The filtrate was concentrated to an oil. The oil was charged on a column containing 150 g of alumina. Elution with a 6:4 hexane–ether mixture gave a light brown, viscous oil. The oil was further chromatographed using hexane as eluent to give a clear oil. The oil was dissolved in hot hexane and cooled at −20° for several days to give a white solid: mp 118–121; ir (Nujol) 5.80 (C=O), 6.20, 6.30, and 6.70 μ (aromatic and aromatic ether); nmr ($CDCl_3$) δ 1.67, 1.71 (2 s, 9, CH_3CBr), 1.80–3.20 (m, 5), 3.50, 3.78, 3.82 (3 s, 9, OCH_3), 4.33 (m, 1, HCPh), 6.03 and 6.17 (2 d, 2, PhH). The data suggests the material to be 2a-bromo-2-methyl-3-(3,4,6-trimethoxyphenyl)-5-(2-bromoisopropyl)cyclohexanone (XXVI).

Reduction of the 3-Trimethoxyphenyl Dibromide XXVI with Lithium Aluminum Hydride.—To a slurry of 0.25 g (0.007 mol) of lithium aluminum hydride in 40 ml of dry ether was added dropwise a solution of 400 mg (0.8 mmol) of the dibromide XXVI in 30 ml of dry ether. The reaction mixture was heated at reflux temperature for 36 hr. The excess hydride was destroyed by adding a saturated solution of sodium sulfate dropwise until the evolution of hydrogen ceased. The resulting mixture was allowed to stir at room temperature for 15 min, the solid salts were filtered, and the ether was dried ($MgSO_4$) and concentrated to give a small amount of clear oil. Vpc separation of the oil gave alcohol XXVIII, a clear viscous liquid: ir (neat) 2.85 (OH), 6.2, and 6.7 μ (aromatic); nmr (CCl_4) δ 0.65 (d, 3), 1.15, 1.40 (2 s, 6), 1.50–2.50 (m, 7), 3.7 (s, 9, OCH_3), and 6.0 (s, 2, PhH).

Oxidation of Alcohol XXVIII.—To a solution of 3.2 g of crude alcohol XXVIII in 75 ml of acetone was added dropwise with stirring 3.0 ml of Jones reagent[26] with control of the temperature below 15° during the addition. The mixture was stirred at room temperature for 2 hr and worked up to give 2.7 g (84%) of light brown oil. Column chromatography followed by preparative thin layer chromatography on the crude material gave a white crystalline solid: mp 113–115°; ir (CCl_4) 5.95 (C=O) and 6.25 μ (aromatic ether); nmr (CCl_4) δ 0.65 (d, 3, J = 6.5 Hz, $HCCH_3$), 1.13, 1.38 (2 s, 6, CH_3), 1.50–2.30 (m, 6), 3.70, 3.75 (2 s, 9, OCH_3), and 6.0 (s, 2, PhH); mass spectrum m/e 318 (parent ion). Equilibration of the 2-methyl group with base gave carone XXIX.

Reaction of *dl*-Carvone with Trimethoxybenzene.—To a solution of 5.0 g (0.033 mol) of *dl*-carvone and 5.6 g (0.033 mol) of trimethoxybenzene in 25 ml of acetic acid was added 30 ml of cold acetic acid saturated with dry HBr. The resulting solution was allowed to stand at 0° for 40 hr and poured into ice–water. The water mixture was extracted with ether, and the ether was washed with water and 10% sodium bicarbonate, dried ($MgSO_4$), and concentrated to give 10.6 g (81%) of 2-methyl-3-(2,4,6-trimethoxyphenyl)-5-(2-bromoisopropyl)cyclohexanone: mp 116–119°; ir (Nujol) 5.90 (C=O), 6.20, and 6.70 μ (aromatic and aromatic ether); nmr (CCl_4) δ 0.65 (d, 3, J = 6 Hz, CH_3CH), 1.75 [s, 6, $(CH_3)_2CBr$), 1.80–3.30 (m, 5), 3.70, 3.80 (2 s, 9, OCH_3), and 6.03 (s, 2, PhH); mass spectrum m/e 398 and 400 (parent ions, ratio 1:1).

Reaction of Ketone XXVII with Sodium Hydroxide.—To a solution of 100 mg of ketone XXVII in 25 ml of ethanol was added 1.0 g of sodium hydroxide in 5 ml of water. The resulting mixture was stirred at room temperature for 24 hr, diluted with water, and filtered to give 56 mg of carone XXIX: mp 95–97°; ir (Nujol) 5.95 (C=O) and 6.20 μ (aromatic ether); nmr (CCl_4) δ 0.68 (d, 3, J = 6 Hz, CH_3CH), 1.20, 1.32 (2 s, 6, CH_3), 1.30–2.00 (m, 6), 3.75 (s, 9, OCH_3) and 6.02 (s, 2, PhH).

Reaction of *trans*-Carvone Tribromide (I) with Hydrogen Bromide in the Presence of Sulfur Dioxide.—To a solution of 50 ml of cold acetic acid saturated with HBr was bubbled in anhydrous SO_2. After SO_2 treatment for *ca.* 5 min, 5.0 g of I in 25 ml of acetic acid was slowly added. The resulting solution was stirred for 1 hr at 0° under SO_2 and poured into ice–water. Ether work-up gave 3.96 g of light brown oil, which was purified by preparative thin layer chromatography to give carvone hydrobromide (II).

In a control experiment, *trans*-carvone tribromide (I) was treated with SO_2 in acetic acid without HBr. Work-up as above gave only starting material.

Registry No.—I, 22249-53-2; II, 22249-54-3; III, 22249-55-4; IV, 22249-56-5; VI, 22249-57-6; VI 2,4-dinitrophenylhydrazone, 22249-58-7; VIII, 22249-59-8; XI, 22249-60-1; XII, 22297-84-3; XII acetate, 22249-61-2; XIV, 22249-62-3; XV, 22249-63-4; XVI, 22249-64-5; XVII, 22249-65-6; XXIII, 22249-66-7; XXIV, 22249-67-8; XXVI, 22249-68-9; XXVIII, 22249-69-0; XXIX, 22297-85-4; 2-chloro-2-methyl-5-(2-chloroisopropyl)cyclohexane-1,3-dione, 22249-70-3; 2a-chloro-2-methyl-3a-acetoxy-5-(2-chloroisopropyl)-cyclohexane, 22249-71-4; 2-methyl-5-(2-bromoisopropyl)cyclohexane-1,3-dione, 22249-72-5; 2-methyl-3-(2,4,6-trimethoxyphenyl)-5-(2-bromoisopropyl)cyclohexanone, 22249-73-6.