1,1-Dihalogenocyclopropanes Derived from Terpenes. The Stereochemistry of Cyclopropylidene Insertion into Carbon–Hydrogen Bonds Adjacent to Alcohols

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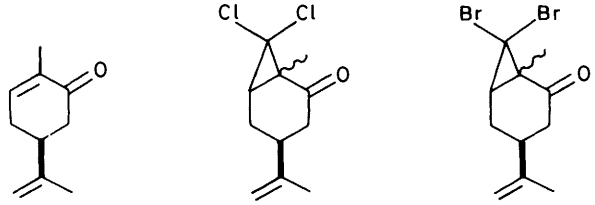
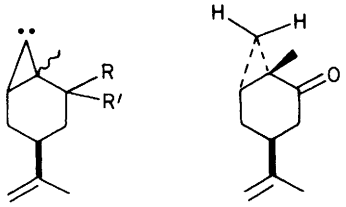
Treatment of the alcohol (**13**) with methyl-lithium in ether leads to the ketone (**5**), whereas (**12**) gives no ketone and the major product is the alcohol (**16**). The formation of (**5**) from (**13**) establishes the requirement for a *syn*-relationship between a C–H bond at the 1-position and C-2′ in the conversion of 1-(2′,2′-dibromocyclopropyl)alkan-1-ols into (cyclopropyl)alkyl ketones.

The reaction of carbenes with terpenes provides a simple means of examining the stereochemistry and regioselectivity of addition of such species to a variety of double bonds. Moreover, the products of dihalogenocarbene addition to terpenes are well suited to an investigation of the effect of intramolecular interactions on a range of transformations of 1,1-dihalogenocyclopropanes. As part of a study of such adducts we now report some aspects of the reactions of dichloro- and dibromocarbenes with carvone.

Carvone (**1**) † is reported to form the adducts (**2**) [1] and (**3**) [2] on reaction with chloroform or bromoform respectively in the presence of aqueous sodium hydroxide and a phase-transfer catalyst; these reactions presumably involve initial Michael addition of the trihalogenomethyl anion, followed by cyclisation and loss of halide ion.

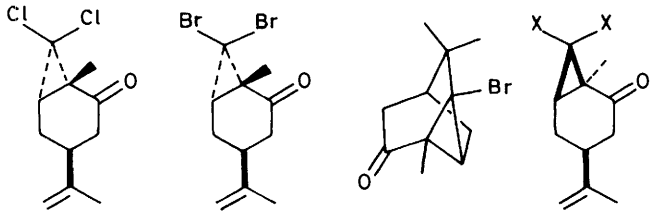


(**1**) (**2**) (**3**)



(**4**) (**5**)

It was expected that modification of the carbonyl group of (**3**) followed by reaction with methyl-lithium would lead to a series of cyclopropylidenes (**4**) or related carbenoids which might undergo insertion into C–H bonds to produce strained polycycles.[3] Although the adducts (**2**) and (**3**) have been the substrates in a number of reactions,[1,4] the stereochemistry of the cyclopropane relative to the isopropenyl-group has apparently not been established; indeed it is not certain that the adducts are single diastereoisomers. Addition of dimethylsulphoxonium methylide to carvone is reported to give a single adduct, characterised as the *trans*-form (**5**);[5] by analogy, the adducts (**2**) and (**3**) may also be expected to be the *trans*-forms (**6**) and (**7**). It is interesting to note, therefore, that the reduction of (**3**) with tri-n-butyltin hydride leads to (**8**) as a minor product (6%).[4] This is derived by intramolecular trapping of an intermediate cyclopropyl radical by the isopropenyl group; at least some of the adduct (**3**) must, therefore, be in the *cis*-form (**9**; X = Br).



(**6**) (**7**) (**8**) (**9**)

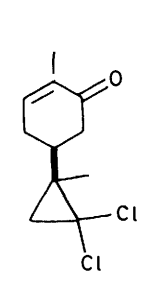
The adduct (**3**) was obtained as previously described by reaction of carvone with bromoform and aqueous sodium hydroxide in the presence of cetrimide as phase-transfer catalyst, and was identical (60 MHz n.m.r. spectroscopy) with an authentic sample.[2,‡] The spectrum showed narrow multiplets at δ 4.56 and 4.87 assigned to the two alkene hydrogens; however, although the sample was homogeneous by t.l.c. and g.l.c., a small additional signal was present at δ 4.70, integrating to *ca.* 20% of each of the other olefinic signals. Moreover, if the product was reduced with a deficiency of lithium aluminium hydride at 20 °C and the unchanged dibromide was separated from alcoholic products by column chromatography, the ketone recovered showed only the two signals at δ 4.56 and 4.87 in the alkene region. We have assigned this product the *trans*-isomer structure (**7**) and have shown that the signal at δ 4.70 is due to the presence of *ca.* 10% of the *cis*-isomer (**9**; X = Br) in the crude product;§ this isomer is reduced rather more rapidly than the *trans*-form. The ^{13}C n.m.r.

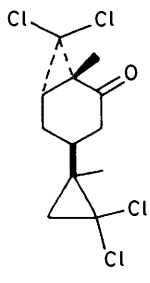
† The work described in this paper was carried out on D-(+)-carvone (**1**) and this form is drawn throughout.

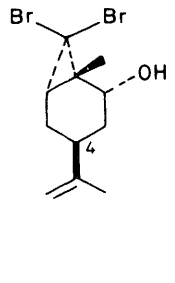
‡ We thank Professor L. Skattebøl and Dr. L. K. Sydnes for kindly providing the spectra of authentic (**3**), (**8**), and (**17**).

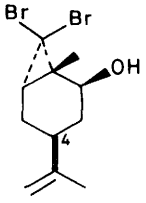
§ The mixture of alcohols obtained above contained three components, two derived from the reduction of some (**7**), the third derived by reduction of the impurity. They could not be separated efficiently by column chromatography, but reoxidation with chromium trioxide–sulphuric acid gave a ketone in which the signal at δ 4.70 was enhanced relative to that in the initial mixture. Repeating this partial reduction–oxidation sequence several times gave pure (**9**; X = Br). The ^1H n.m.r. spectrum of (**9**; X = Br) included a triplet of triplets (*J* 13.6 and 3.9 Hz) assigned to 4-H; the coupling constants are in agreement with those expected for the pseudo-half-chair form of (**9**; X = Br), with an equatorial isopropenyl group (**9a**) (see Scheme 1). As with (**9**; X = H),[6] reduction of (**9**; X = Br) with $LiAlH_4$–ether gave a single product characterised as (**18**; X = Br); the methine hydrogen adjacent to the alcohol showed coupling of 11.4 and 7.2 Hz to the adjacent hydrogens, in agreement with a pseudo-chair form with an equatorial hydroxy group (**18a**) (see Scheme 1).

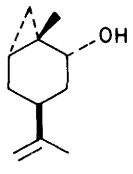
spectrum of (**7**) showed eleven signals as expected for two primary, three secondary, two tertiary, and four quaternary carbons. The 360 MHz ^{1}H n.m.r. spectrum showed two methyl signals—a singlet at δ 1.46 and a double triplet at δ 1.75 (*J* 1.5, 0.7 Hz). The two alkene hydrogens at δ 4.56 and 4.87 were shown by double irradiation to be allylically coupled to the methyl group at δ 1.75 and to a proton appearing as a broad pentuplet (*J ca.* 4.5 Hz, 1 H) at δ 2.66, which is assigned to 4-H. A sharp double doublet at δ 1.83 (*J* 9, 3.5 Hz, 1 H) was assigned to 6-H and was shown by double irradiation to be coupled to a hydrogen appearing as a double double doublet (*J* 15, 5, 3.5 Hz, 1 H) at δ 2.0 and to one appearing as a double double double double doublet (*J* 15, 9, 4.5, 1.5, 0.7 Hz, 1 H) at δ 2.46, assigned to the two non-equivalent protons on C-5. The remaining hydrogens, those on C-3, appeared as a tented pair of double double doublets (*J* 0.7, 4.5, 15 and 1.5, 4.5, 15 Hz respectively) at δ 2.37 and 2.47 which partly overlapped the signal centred at δ 2.46. The fact that 4-H showed four approximately equal couplings of 4.5 Hz to the four vicinal hydrogens indicates four similar dihedral angles. Examination of a model of the *cis*-isomer (**9**; X = Br) shows only one conformation in which this is the case, involving both cyclopropane and isopropenyl groups in *syn*-pseudoaxial positions; this seems unlikely as the latter groups would be extremely close to the *endo*-bromine. This conformation also requires equal dihedral angles between 6-H and the two hydrogens on C-5; in practice the couplings are very different. In contrast, examination of a model of the *trans*-isomer (**7**) indicates that in the conformation (**7a**)* (see Scheme 1) 4-H has four equal dihedral angles to the hydrogens on C-3 and C-5 while 6-H has dihedral angles of 0° and 120° to the hydrogens on C-5, in agreement with the observed coupling constants of 9 and 3.5 Hz. The assignment of *trans*-stereochemistry as in (**7**) is confirmed chemically below.

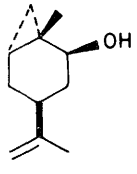

(**10**)


(**11**)


(**12**)

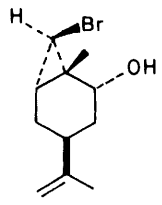

(**13**)

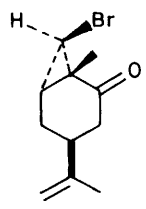

(**14**)

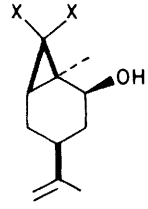

(**15**)

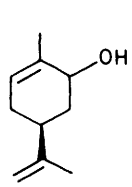
The adduct (**2**) was obtained (60%) by reaction of carvone with two equivalents of chloroform and excess of sodium hydroxide in the presence of triethylbenzylammonium chloride (*TEBA*), conditions similar to those described by Sydnes.[1] The 60 MHz ^{1}H n.m.r. spectrum of (**2**) was essentially identical with that of the dibromocarbene analogue although the peak at δ 4.70 was even smaller in the chloro case; we again assign the major adduct the *trans*-stereochemistry (**6**). The same product was obtained when carvone was treated with one equivalent of chloroform and excess of base in the presence of cetrimide as catalyst. However when the reaction was carried out with four equivalents of chloroform, only small amounts of (**6**) were obtained; instead the major product was the adduct at the isopropenyl group (**10**) (50%) [δ_H: 6.81 (br s, 1 H), 2.1—2.75 (m, 5 H), 1.8 (s, 3 H), 1.27 (s, 3 H), and 1.25 (s, 2 H)]; the ^{13}C n.m.r. spectrum of this compound indicated that it was present as a mixture of diastereoisomers. A minor product was the bis-adduct (**11**). Phase-transfer reactions are known to be somewhat dependent on the exact reaction conditions,[7] and the formation of products apparently derived from trihalogenomethyl anion [such as (**6**)] or dihalogenocarbene [such as (**10**)] can be controlled by varying the catalyst.[8] However, the change in mechanism in the present case is surprising and is being investigated further in related systems.

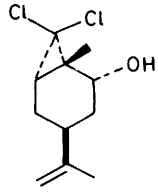
Reduction of (**7**) with lithium aluminium hydride is reported to occur efficiently at the carbonyl group,[2] but the stereochemistry of the product is not described; reduction with sodium borohydride occurs only in very low yield. Careful reduction of (**7**) with lithium aluminium hydride in ether at 20 °C led to two dibromo alcohols in the ratio *ca.* 3:1. Oxidation of either with CrO_3–H_2SO_4–aqueous acetone led to a ketone identical (n.m.r., t.l.c., and g.l.c.) with (**7**), and which on being reduced again with $LiAlH_4$ gave the same mixture of dibromo alcohols; this sequence shows that the ketone is not a mixture of diastereoisomers and establishes that the alcohols are epimers about C-2, *i.e.* (**12**) and (**13**), with the same stereochemistry at C-4. The major alcohol was assigned the stereochemistry shown in (**12**) on the basis of reduction from the face of the molecule away from the dibromocyclopropane. This assignment is confirmed below using chemical methods; it is, however, the reverse of the stereochemical preference assigned to the reduction of the non-brominated ketone, (**5**), which is reported to give a 1:4 mixture of (**14**) and (**15**).[6]


(**16**)


(**17**)


(**18**)


(**19**)

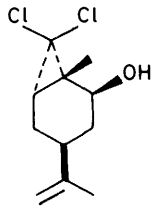

(**20**)

The alcohol (**12**) showed a characteristic double doublet, *J* 11 and 7.2 Hz, for the methine hydrogen on C-2. It could be further reduced to the monobromo alcohol (**16**) on being stirred for 3 h at 20 °C with additional lithium aluminium hydride in ether. The mono-bromide showed a doublet at δ 3.15 (*J* 4.5 Hz) typical of an *exo*-bromocyclopropane, but the hydrogen on C-2 now

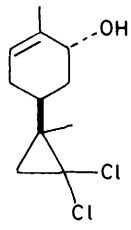
* The assignment of a pseudo-axial position to the isopropenyl group is perhaps surprising, but the preferred conformation is found to change on removal of the 7-bromines to give (**5**) (see below).

appeared as a triplet (J 5 Hz);* it was oxidised by chromium trioxide–sulphuric acid to (**17**), the n.m.r. spectrum of which was identical with that of a sample prepared by direct reduction of the dibromocyclopropane in (**3**)[2,]‡ with tributyltin hydride. The monobromide (**16**) was, in turn, further reduced by $LiAlH_4$–ether in 20 h at 20 °C to give (**14**). Oxidation of (**14**) with CrO_3–H_2SO_4–aqueous acetone gave the ketone (**5**)† which was shown to be different from the isomer (**9**; X = H) obtained by Simmons-Smith reaction on (**19**),[6,9] followed by oxidation. This sequence confirms that the isopropenyl group in (**7**), (**12**), and (**13**) is *trans* to the cyclopropane. The minor alcohol (**13**), m.p. 95—97 °C, showed in its ^1H n.m.r. spectrum the expected two methyl signals, a singlet at δ 1.42 and a multiplet at δ 1.68, and two alkene multiplets at δ 4.67 and 4.69, together with one exchangeable hydrogen. In addition, three well dispersed single hydrogen multiplets appeared at δ 3.93 (dd, J 12, 4 Hz), 1.28 (q, J 12 Hz), and 1.73 (dddd, J 12, 4, 3, 0.7 Hz) which were assigned to 2-H, 3a-H, and 3e-H (J_{23e} = 4, J_{23a} = 12, J_{3e3e} = 12, J_{3a4} = 12, J_{3e4} = 3). The remaining four hydrogens appeared as very complex signals centred at 2.21 (4-H), 1.97 (5e-H), 1.66 (5a-H), and 1.60 (6-H), but the spectrum could be analysed in terms of couplings of J_{45e} = 7, J_{45a} = 9, J_{46} = 0, J_{5e5a} = 14, J_{5e6} = 0, and J_{5a6} = 9 Hz; computer simulation gave a good match with the observed spectrum. These couplings are consistent with the half-chair form (**13a**) (see Scheme 1).

Reduction of (**6**) with lithium aluminium hydride in ether gave a mixture of two dichloro alcohols (**20**), and (**21**), which had n.m.r. spectra essentially identical with those of (**12**) and (**13**), respectively.



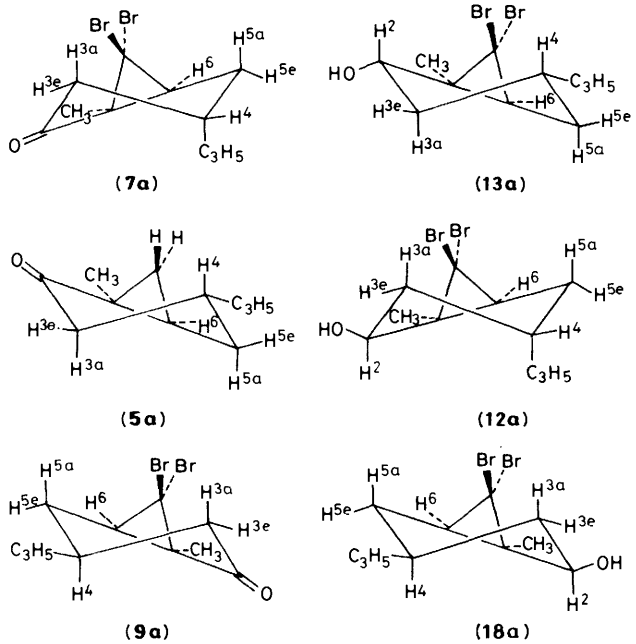
(**21**)



(**22**)

Proof that the alcohol (**21**) [and therefore (**13**)] has the stereochemistry shown at the 2-position was obtained by addition of dichlorocarbene to (**19**).[9] Dichlorocarbene has been reported to add to an alcohol of gross structure (**19**) to give a mixture of adducts at each double bond, but the mixture was not separated and the stereochemistry of the starting alcohol was not discussed.[10] Reaction of (**19**) with chloroform and aqueous sodium hydroxide in the presence of cetrimide gave a mixture containing several components. One of the major components crystallised partly on standing and was shown to be identical with (**21**). The second major component was not obtained completely free of (**21**) in this manner or by column chromatography; however, on oxidation with activated manganese dioxide it was converted into a ketone while (**21**) remained unchanged, and the two components were then separated by column chromatography. The ketone was identical with (**10**) obtained above.§ Since reduction of (**6**) with $LiAlH_4$–ether gave (**21**), identical by n.m.r. and t.l.c. with the alcohol present in the above mixture from dichlorocarbene addition to (**19**), the stereochemistry at C-4 in (**12**), (**13**), (**20**), and (**21**) has been established above, and the stereochemistry of (**19**) is known, this sequence proves the stereochemistry at C-2 of (**21**), and hence of (**20**), (**12**), and (**13**). Two observations may be made as a result of this series of reactions. Firstly, addition of dichlorocarbene to (**19**) under phase-transfer conditions to produce (**21**) occurs from the side opposite the alcohol, unlike the situation in a recent report of alcohol directed *syn*-addition.[11] Secondly, the major alcohols from the reduction of (**6**) and (**7**) with lithium aluminium hydride are (**20**) and (**12**), whereas the major isomer from reduction of (**5**) has been assigned as (**15**);[6] this reversal of selectivity was indeed confirmed by showing that (**14**) obtained by reduction of (**12**) was identical with the minor alcohol from the reduction of (**5**).

The reaction of (dibromocyclopropyl)alkanols (**23**) with methyl-lithium in ether has been reported to lead to cyclopropyl substituted aldehydes and ketones, in a reaction which apparently proceeds by insertion of an intermediate cyclopropylidene (**24**), or a related carbenoid, into a C–H bond adjacent to the alcohol[12] (Scheme 2). The reaction is important in relation to the wide variety of known transformations of cyclopropylidenes, and does not occur when n = 2 or 3.[13]



Scheme 1.

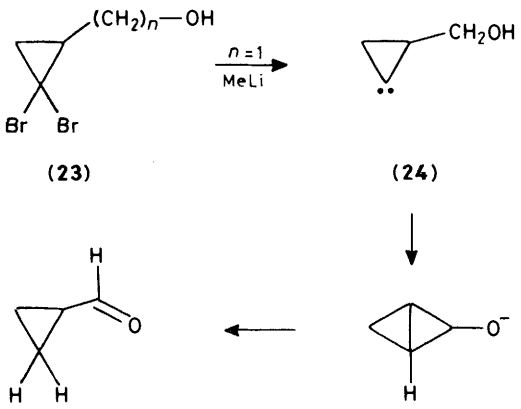
* The change in the coupling constants for 2-H may reflect a change in the preferred conformation of this system on removal of the *endo*-bromine. The signals for the dinitrobenzoate of (**12**) were not completely resolved even at 360 MHz. However those for 2-H, 3e-H, and 3a-H were identified and couplings are consistent with a half-chair conformation (**12a**) (see Scheme 1) with the alcohol equatorial and the isopropenyl group axial whereas those for 2-H of (**16**) [and for (**14**)] are in agreement with a half-chair form with the alcohol in a pseudo-axial position and the isopropenyl group pseudo-equatorial.

† The n.m.r. of (**5**) could be interpreted in terms of a half-chair form with the isopropenyl group equatorial (**5a**) (see Scheme 1). Thus 6-H (δ 1.49) showed couplings of 3.5 and 3 Hz to the pseudo-axial (δ 1.84) and pseudo-equatorial (δ 2.04) hydrogens on C-5. These, in turn, showed couplings of 11.4 and 4 Hz respectively to the (axial) hydrogen on C-4.

These couplings are rather different from those seen in (**7**) and, presumably, there is a change in preferred conformation from (**7a**) to (**5a**) owing either to the presence or absence of a bromine at C-7.

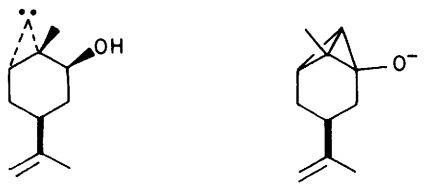
‡ See footnote on p. 1379.

§ Reduction of (**10**) with $LiAlH_4$–ether gave a mixture of two components which had very similar R_F values; the overall ^1H n.m.r. spectrum suggested a mixture of diastereoisomers of (**22**) was present and the signals were all present in the spectrum of the crude product from the reaction of (**19**) with chloroform and base.



Scheme 2.

Treatment of (**12**) with methyl-lithium in ether at 20 °C leads to (**16**) as the major component of a complex mixture; this is apparently obtained by lithium–halogen exchange at the dibromide followed by inter- or intra-molecular hydrogen transfer. However, reaction of (**13**) with methyl-lithium gave the ketone (**5**), which was identical with a sample obtained above, as the only major product. The formation of (**5**) can be explained in terms of an insertion by an intermediate carbene (carbenoid) (**25**) into the C(2)–H bond which, in this isomer, is *syn* to the carbene centre. The product, (**26**), would then undergo ring opening on work-up to give the cyclopropyl ketone.



(**25**) (**26**)

Experimental

I.r. spectra were obtained for liquid films or KBr discs on a Perkin-Elmer 257 spectrometer. N.m.r. spectra were recorded at 60 MHz on a Varian EM360 or at 360 MHz on a Bruker spectrometer; ^{1}H n.m.r. spectra were run in deuteriochloroform or carbon tetrachloride using tetramethylsilane as internal standard and ^{13}C n.m.r. spectra were run in deuteriochloroform (we thank Dr. I. H. Sadler of Edinburgh University for running the 360 MHz spectra and some highfield ^{13}C n.m.r. spectra). Mass spectra were obtained on an A.E.I. instrument.

Chromium trioxide–sulphuric acid refers to a solution prepared from chromium trioxide (4.5 g), sulphuric acid (4 ml), and water (22 ml).

Preparation of 8,8-*Dibromo*-1-*isopropenyl*-5-*methylbicyclo*[4.1.0]*heptan*-2-*one*.—D-(+)-Carvone (40 g, 0.27 mol), bromoform (80 g, 0.32 mol), cetrimide (0.5 g), and aqueous sodium hydroxide (100 ml; 10M) were stirred together at 50 °C for 6 h and then at 20 °C for 60 h. The products were extracted three times with ether (100 ml) and the organic extract was dried ($MgSO_4$) and the solvent removed at 14 mmHg. Column chromatography over silica gave unchanged bromoform and then, on elution with chloroform, the dibromide (**7**) (62 g, 72.5%) which contained *ca.* 10% of an impurity [this was shown by the presence of a broad singlet at δ 4.76 integrating to *ca.* 20% of each of the alkene signals of (**7**) which appeared at 4.56 and 4.87. The signal is shown below to be due to two hydrogens in the impurity (**9**; X = Br)]. The impurity was removed by treating the dibromide with sufficient lithium aluminium hydride in ether at 20 °C to cause the signal at δ 4.76 to disappear. Column chromatography as above then gave pure (**7**) and a mixture of alcohols; this mixture was used (see below) to regenerate and identify the impurity. *Compound* (**7**)[2] showed $\delta_H(CCl_4)$ 1.46 (3 H, s), 1.75 (3 H, dt, *J* 1.5, 0.7 Hz), 1.83 (1 H, dd, *J* 9, 3.5 Hz), 2.0 (1 H, ddd, *J* 15, 5, 3.5 Hz), 2.37 (1 H, ddd, 15, 4.5, 0.7 Hz), 2.46 (1 H, ddddd, *J* 15, 9, 4.5, 1.5, 0.7 Hz), 2.47 (1 H, ddd, *J* 15, 4.5, 1.5 Hz), 2.66 (1 H, broad pentuplet, *J* 4.15 Hz), 4.56 (1 H, narrow multiplet), and 4.87 (1 H, narrow multiplet); δ_C 201.7 (s), 145.6 (s), 111.1 (t), 41.7 (t), 40.2 (s), 39.1 (d), 36.5 (d), 35.3 (s), 24.8 (t), 21.7 (q), and 21.0 (q); $\nu_{max.}$(film) 2 900, 1 705, and 1 645 cm^{-1}.

Reaction of (**7**) *with Lithium Aluminium Hydride*.—Lithium aluminium hydride (236 mg, 0.0062 mmol) was added to stirred (**7**) (4.0 g, 0.024 mol) in ether (100 ml). The reaction was followed by t.l.c. and when no starting material remained (20 min) excess of reagent was destroyed by careful addition of water. The products were washed with water (100 ml) and the aqueous layer was re-extracted with ether (50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed at 14 mmHg to give an oil which showed two major peaks on g.l.c. in the ratio *ca.* 3:1 and two major spots on t.l.c. The oil underwent partial crystallisation on addition of light petroleum (b.p. 40—60 °C). The crystals were recrystallised from petroleum to give 7,7-*dibromo*-trans-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-trans-2-*ol* (**13**), m.p. 95—97 °C (Found: M^+, 321.9610. Calc. for $C_{11}H_{16}Br_2O$: *M*, 321.9568) which showed δ_H 1.28 (1 H, q, *J* 12 Hz), 1.42 (3 H, s), 1.68 (3 H, narrow multiplet), 1.60 (1 H, m), 1.66 (1 H, m), 1.73 (1 H, dddd, *J* 12, 4, 3, 0.7 Hz), 1.97 (1 H, m), 2.21 (1 H, m), 3.93 (1 H, dd, *J* 12, 4 Hz), 2.08 (1 H, br s), 4.67 (1 H, narrow m), and 4.69 (1 H, narrow m); δ_C 148.5 (s), 109.3 (t), 70.0 (d), 48.5 (s), 39.2 (d), 36.4 (d), 35.9 (t), 31.8 (s), 26.0 (t), 20.7 (q), and 20.2 (q); $\nu_{max.}$ 3 400, 2 950, and 1 650 cm^{-1}. Column chromatography of the mother liquor (silica, eluting with chloroform) gave the second major component 7,7-*dibromo*-trans-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-cis-2-*ol* (**12**) (2.4 g, 60%) as an oil (Found: M^+, 321.9569. Calc. for $C_{11}H_{16}Br_2O$: *M*, 321.9568) which showed δ_H 1.3 (1 H, m), 1.4 (3 H, s), 1.7 (3 H, s), 2.0 (6 H, m), 3.7 (1 H, m), 4.6 (1 H, s), and 4.8 (1 H, s); $\nu_{max.}$ 3 400, 2 900, and 1 650 cm^{-1}, together with additional (**3**) (total 1.1 g, 28%), and a trace (22 mg) of a minor component identical (g.l.c. and n.m.r.) with (**16**) (see below).

The dibromide (**12**) was converted into its 3,5-dinitrobenzoate (Found: M^+, 515.9555. Calc. for $C_{18}H_{18}Br_2N_2O_6$: *M*, 515.9532) which showed δ_H (360 MHz), 9.2 (3 H, m), 5.5 (1 H, dd, *J* 11.05, 7 Hz), 4.94 (1 H, q, *J* 1 Hz), 4.76 (1 H, br s), 2.46 (2 H, m, inc. *J* 12, 3, 2 Hz), 2.2 (1 H, dddd, *J* 13.5, 7, 4.5, 2 Hz), 1.93 (1 H, ddd, *J* 13.5, 11.05, 4 Hz), 1.78 (2 H, m), 1.81 (3 H, narrow m), and 1.48 (3 H, s).

Oxidation–Reduction of (**12**).—(*a*) Chromium trioxide–sulphuric acid (1 ml) was added dropwise to (**12**) (200 mg) in acetone over 5 min at 20 °C. The products were extracted with chloroform and the solvent was removed at 14 mmHg to give an oil which was one product on t.l.c. and was purified by column chromatography (190 mg, 95%) and shown to be identical (n.m.r., g.l.c., and t.l.c.) with (**7**).

(*b*) Lithium aluminium hydride (21 mg, 0.55 mmol) was added slowly to (**7**) (from above experiment) in dry ether at 20 °C and the reaction was followed by t.l.c. After 20 min the products were worked up as above to give an oil which was a mixture of two products by t.l.c. These were separated by column chromatography and found to be (**12**) (60 mg) and (**13**)

(40 mg) identical (t.l.c. and n.m.r.) with authentic samples; yield 100 mg (53%).

Oxidation–Reduction of (**13**).—(*a*) Chromium trioxide–sulphuric acid (1 ml) was added over 5 min to (**13**) (200 mg) in acetone (5 ml). Work-up as above gave an oil which was purified by column chromatography and found to be identical (n.m.r., g.l.c., and t.l.c.) with (**7**) obtained above (190 mg, 95%). (*b*) Lithium aluminium hydride (21 mg) was added to (**7**) (190 mg) [from (*a*)] in ether (5 ml) and the reaction was followed by t.l.c. After 15 min no starting material remained and the products were worked up as above to give an oil which was separated by column chromatography into (**12**) (80 mg) and (**13**) (40 mg) (combined yield 63%).

7,7-*Dibromo*-cis-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-2-*one*.—The mixture of alcohols obtained by reduction of crude (**7**) with a deficiency of $LiAlH_4$ (see second experiment) contained (**12**) and (**13**) together with a third alcohol of intermediate R_F value. The mixture was reoxidised to ketones by treatment with an excess of chromium trioxide–sulphuric acid for 5 min at 20 °C, followed by extraction with ether. The ketone mixture obtained was identical with (**7**) by t.l.c., but showed a marked increase in the signal at δ 4.70 compared with those at 4.56 and 4.87 (*ca.* a four-fold increase). The sequence of reduction with a deficiency of lithium aluminium hydride, column chromatography, and re-oxidation was repeated several times to give (**9**; X = Br) (Found: M^+, 319.9427. Calc. for $C_{11}H_{14}Br_2O$: *M*, 319.9411) which showed δ_H 4.79 (1 H, pentuplet, *J* 1 Hz), 4.74 (1 H, br s), 2.45 (1 H, ddd, *J* 15.0, 3.9, 2.7 Hz), 2.39 (1 H, tt, *J* 13.6, 3.9 Hz), 2.32 (1 H, ddd, *J* 17.5, 3.9, 2.7 Hz), 2.23 (1 H, dd, *J* 17.5, 13.6 Hz), 2.0 (1 H, dd, *J* 9.9, 4.15), 1.73 (3 H, br s), 1.67 (1 H, ddd, *J* 15.0, 13.6, 4.15 Hz), and 1.53 (3 H, s); $\nu_{max.}$ 3 090, 1 700, 1 640, and 765 cm^{-1}.

Reduction of the ketone with lithium aluminium hydride in ether for 5 min at 20 °C as above gave a single product characterised as 7,7-*dibromo*-cis-4-*isopropenyl*-1-*methylbicyclo*-[4.1.0]*heptan*-cis-2-*ol* (**18**; X = Br) (Found: M^+, 321.9569. Calc. for $C_{11}H_{16}Br_2O$: *M*, 321.9568) which showed δ_H 4.73 (1 H, pentuplet, *J* 1.5 Hz), 4.70 (1 H, narrow m), 4.15 (1 H, dd, *J* 11.4, 7.2 Hz), 2.24 (1 H, dddd, *J* 14.0, 10.3, 4.5, 2 Hz), 1.86 (2 H, m), 1.76 (1 H, dd, *J* 10.3, 3.3 Hz), 1.70 (3 H, dd, *J* 1.5, 1 Hz), 1.61 (3 H, s), 1.58 (1 H, dt, *J* 11.4, 13 Hz), and 1.42 (1 H, ddd, *J* 14, 13, 3.3 Hz); $\nu_{max.}$ 3 420, 3 080, 1 645, and 760 cm^{-1}.

Reduction of (**12**) *to* (**16**).—The dibromo alcohol (**12**) (485 mg) was stirred with lithium aluminium hydride (100 mg) in ether (15 ml) for 20 min at 20 °C. G.l.c. showed complete reaction had occurred to give a single major product of shorter retention time. Work-up as before gave exo-7-*bromo*-trans-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-cis-2-*ol* (**16**) (320 mg) (Found: M^+, 224.0450. Calc. for $C_{11}H_{17}BrO$: *M*, 244.0463) which showed δ_H 1.3 (3 H, s), 1.4 (2 H, m), 1.7 (3 H, s), 2.0 (4 H, m), 3.15 (1 H, d, *J* 4.5 Hz), 3.4 (1 H, br s), 4.04 (1 H, t, *J* 5 Hz), and 4.7 (2 H, br s); $\nu_{max.}$ 3 350, 2 900, 1 650, 1 450, and 900 cm^{-1}.

Oxidation of (**16**).—Compound (**16**) (55 mg) in acetone (1 ml) was treated with Jones reagent (0.5 ml) for 5 min as before. Work-up gave a ketone (45 mg) the n.m.r. spectrum of which was identical with that shown by authentic (**17**).‡

Reaction of (**12**) *with Methyl-lithium*.—Methyl-lithium (2 ml; 1.25M) was added over 1 min to compound (**12**) (500 mg) stirred in ether (10 ml) at −40 °C. After 2 min the products were quenched carefully with water (5 ml) and the organic layer was separated and dried and the solvent was removed at 14 mmHg to give a colourless oil (315 mg) which showed at least six spots on t.l.c.; the i.r. of the oil showed only a very small peak in the carbonyl region. Preparative t.l.c. gave three components. The first (22 mg) was not obtained completely pure and showed a complex mass spectrum with ions at *m/z* 162, 163, 164, and 165; however, n.m.r. spectroscopy showed that it was not (**5**). The second (55 mg) was identical (n.m.r. and t.l.c.) with starting material. The third and major component was exo-7-*bromo*-trans-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-cis-2-*ol* (**16**) (144 mg, 38%) which was identical (n.m.r.) with a sample obtained above by reduction of (**12**).

Reaction of (**13**) *with Methyl-lithium*.—Methyl-lithium (3 ml; 1.25M) was added over 1 min to (**13**) (444 mg) and stirred in ether (10 ml) at −40 °C. After 2 min the products were worked up as above to give an oil (215 mg) which showed one major spot on t.l.c. and appeared by n.m.r. spectroscopy to consist of one major component. Preparative t.l.c. gave the *ketone* (**5**) (160 mg, 71%) the 60 MHz n.m.r. spectrum of which was essentially identical with that of the crude reaction product; δ_H (360 MHz): 4.70 (1 H, pentuplet, *J* 1.5 Hz), 4.67 (1 H, br s), 2.27—2.36 (2 H, complex), 2.04 (1 H, dddd, *J* 13.5, 4, 3, 1.5 Hz), 1.91 (1 H, dd, *J* 21, 12.8 Hz), 1.84 (1 H, ddd, *J* 13.5, 11.4, 3.5 Hz), 1.49 (1 H, dddd, *J* 7.9, 5.4, 3.5, 3 Hz), 1.29 (1 H, t, *J* 5.4 Hz), and 0.78 (1 H, dd, *J* 7.9, 5.4 Hz). A second component was characterised as unchanged starting material (20 mg).

Reduction of (**5**).—The ketone (**5**), obtained as above (120 mg) was reduced with lithium aluminium hydride (10 mg) in ether (10 ml) for 5 min at 20 °C. Work-up as before gave an oil (110 mg) with was two spots on t.l.c. The n.m.r. spectrum was consistent with the reported 4:1 mixture of alcohols (**15**) and (**14**).

Reduction of (**16**).—Compound (**16**) (350 mg) was stirred for 20 h at 20 °C in ether with lithium aluminium hydride (50 mg). G.l.c. showed complete reaction of the starting material and the formation of one product, with a lower R_t. This was identical (n.m.r. and t.l.c.) with (**14**). Oxidation with an excess of chromium trioxide–sulphuric acid gave (**5**).

cis-4-*Isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-cis-1-*ol*.—Diiodomethane (58 g) was added to a stirred suspension of zinc–copper couple (18 g, 0.275 mol) in ether (125 ml) in the presence of a trace of iodine (0.1 g). After refluxing for 1 h, *cis*-carveol (**19**)[9] (15 g, 0.1 mol) in ether (20 ml) was added over a period of 10 min. The mixture was refluxed for 2.5 h and then stirred for 18 h at 20 °C; it was then washed with saturated ammonium chloride (50 ml) and the aqueous extract was washed twice with ether (50 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogencarbonate and dried and the solvent was removed at 14 mmHg to give an oil which contained starting material and, on the basis of n.m.r. and g.l.c. evidence, one major product. Bulb-to-bulb distillation at 0.1 mmHg gave an oil which partly crystallised on standing to give a very low melting solid characterised as the title alcohol (**18**; X = H)[6] (Found: M^+, 166.1342. Calc. for $C_{11}H_{18}O$: *M*, 166.1358) which showed δ_H 4.52 (2 H, br s), 3.83 (1 H, dd, *J* 11, 6 Hz), and 2.3—0.2 [15 H, complex, including 1.6 (3 H, s), and 1.18 (3 H, s)] (distilled yield 12.7 g, 1:1.7 mixture of starting material and product).

Oxidation of (**18**; X = H) *with Chromium Trioxide*.—A portion of the above distillate (2.0 g) in acetone (5 ml) was treated with chromium trioxide (0.5 g) and sulphuric acid (0.5 ml) in water (2.5 ml) at 0 °C. After 30 min the products were

‡ See footnote† on page 1379.

treated with water (50 ml) and extracted twice with ether (50 ml). The combined organic layers were washed with saturated aqueous sodium hydrogencarbonate and dried. Removal of the solvent at 14 mmHg gave an oil which contained carvone and one major product with a longer retention time. Column chromatography gave the latter, cis-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-2-*one*,[6] δ_H 4.79 (1 H, t, *J* 1.5 Hz), 4.73 (1 H, narrow m), 2.1—2.6 (4 H, m), 1.5—1.7 (2 H, m), 1.74 (3 H, s), 1.23 (3 H, s), and 1.0—1.2 (2 H, m).

Reaction of Carvone with Chloroform and Sodium Hydroxide under Phase-transfer Conditions.—(*a*) D-(+)-Carvone (40 g, 0.267 mol), chloroform (67 g, 0.562 mol), and TEBA (2 g) were stirred at 25 °C and aqueous sodium hydroxide (40 g in 80 ml) was added at such a rate that the temperature did not exceed 45 °C. The reaction was stirred for 4 days at 25 °C and then poured into water (300 ml) and extracted with ether (2 × 200 ml). The solvent was removed from the dried organic layer at 14 mmHg to give a brown oil which was distilled to give 7,7-*dichloro*-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-2-*one* (**6**);[1] δ_C 204.5, 146.4, 111.6, 42.7, 41.8, 39.8, 36.5, 32.4, 23.3, 21.4, and 19.2.

(*b*) Carvone (20 g, 0.133 mol), chloroform (16 g, 0.134 mol), and cetrimide (0.5 g) were stirred at 25 °C and sodium hydroxide (30 g) in water (60 ml) was added at such a rate that the temperature did not exceed 30 °C. After the mixture had been stirred for 3 days the products were worked up as before and the oil produced was distilled at 0.55 mmHg. The first fraction consisted of unchanged chloroform and carvone. The second, b.p. 90—110 °C was a 3:1 mixture of (**6**) and carvone. The third fraction, b.p. 115—123 °C was (**6**) (11.3 g, 39%) together with a trace of the isomer (**10**). The residue (10.4 g) contained some (**6**) (n.m.r. evidence) but, in addition, products which showed only highfield n.m.r. signals.

(*c*) Carvone (40 g, 0.267 mol), chloroform (96 g, 0.803 mol), and cetrimide (1 g) were stirred at 25 °C and aqueous sodium hydroxide (40 g, in 80 ml) was added over 10 min. After 15 min the reaction began to reflux; when the exothermic reaction was complete the products were stirred for a further 24 h, when g.l.c. indicated the presence of two components with long retention times together with some starting material. Further chloroform (96 g) was added and the products were stirred at 65—70 °C for 72 h, and then poured into water (400 ml) and extracted with dichloromethane (3 × 200 ml). The combined organic layers were washed with 2M-sulphuric acid (200 ml), dried, and concentrated at 14 mmHg. Distillation of the residue gave carvone (12.5 g) followed by two fractions, b.p.s 80—100 °C and 125—130 °C at 0.3 mmHg. Both these fractions contained some carvone together with (**6**) and a major component (ratio *ca.* 1:7) which were separated by chromatography over silica, eluting with benzene. The major component was characterised as 5-(2,2-*dichloro*-1-*methylcyclopropyl*)-2-*methylcyclohex*-2-*en*-1-*one* (**10**) (26.5 g, 50%) which showed $\delta_H(CDCl_3)$ 6.81 (1 H, br s), 2.1—2.75 (5 H, m), 1.8 (3 H, br s), 1.27 (3 H, s), and 1.25 (2 H, s); $\nu_{max.}$ 760 and 1 675 cm^{-1}; δ_C 201.8, 201.5, 147.7, 147.4, 138.7, 138.5, 70.7, 70.4, 45.1, 44.6, 44.1, 35.7, 32.2, 31.7, 31.5, 19.3, and 18.9. This compound was characterised as its 2,4-dinitrophenylhydrazone, m.p. 219—221 °C (Found: C, 49.4; H, 4.3; N, 13.65. Calc. for $C_{17}H_{18}N_4Cl_2O_4$: C, 49.39; H, 4.36; N, 13.56) which showed δ_H 9.17 (1 H, d, *J* 2 Hz), 8.38 (1 H, dd, *J* 9 Hz), 8.02 (1 H, d, *J* 9 Hz), 6.32 (1 H, br s), 2.15—3.2 (6 H, m), 2.04 (3 H, br s), 1.37 (3 H, s), and 1.33 (2 H, s); $\nu_{max.}$ 760, 1 350, 1 510, 1 590, and 1 615 cm^{-1}. The residue was recrystallised from ethanol to give 4-(2,2-*dichloro*-1-*methylcyclopropyl*)-7,7-*dichloro*-1-*methylbicyclo*[4.1.0]*heptan*-2-*one* (**11**) (7.5 g, 9%) (Found: C, 45.6; H, 4.35. Calc. for $C_{12}H_{14}Cl_4O$: C, 45.57; H, 4.43) which showed δ_H 1.8—2.6 (6 H, complex), 1.52 (3 H, s), 1.26 (3 H, s), and 1.23 (2 H, s); δ_C 203.9, 67.0, 66.7, 41.5, 37.9, 37.0, 36.1, 32.8, 32.4, 21.6, 18.8, and 15.5; $\nu_{max.}$ 1 710 and 760 cm^{-1}.

Reduction of 7,7-*Dichloro*-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-2-*one.*—The dichloride (**16**) (2.0 g) in ether (50 ml) was treated with lithium aluminium hydride (0.16 g) and the reaction was monitored by t.l.c. After 15 min no starting material remained; the products were treated carefully with water (50 ml) and the aqueous layer was washed with ether (50 ml). The combined organic layers were dried and the solvent was removed at 14 mmHg to give an oil which showed two major peaks on g.l.c. in the ratio 4:1, and two spots on t.l.c. The components were separated by column chromatography (silica, eluting with chloroform) and identified as 7,7-*dichloro*-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-cis-2-*ol* (1.13 g, 56%) (Found: M^+, 234.0556. Calc. for $C_{11}H_{16}Cl_2O$: *M*, 234.0578) which showed δ_H 4.88 (1 H, br s), 4.7 (1 H, br s), 3.88 (1 H, dd, *J* 12, 7 Hz), 1.2—2.5 [13 H, m—including 1.47 (3 H, s), and 1.75 (3 H, br s)]; $\nu_{max.}$ 3 400, 2 940, 1 640, and 730 cm^{-1}; and 7,7-*dichloro*-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-trans-2-*ol* (0.16 g, 8%) (Found: C, 55.95; H, 6.65; M^+, 234.0580. Calc. for $C_{11}H_{16}Cl_2O$: C, 56.17; H, 6.8; M^+, 234.0578) which showed δ_H 4.79 (1 H, br s), 4.77 (1 H, br s), 4.04 (1 H, dd, *J* 11, 4 Hz), 1.25—2.5 [13 H, m, including 1.43 (3 H, s), and 1.71 (3 H, br s)]; $\nu_{max.}$ 3 350, 2 915, 1 640, and 810 cm^{-1}. In addition a third fraction (93 mg) was obtained which was eluted after both of the major products; oxidation of this fraction with chromium trioxide–sulphuric acid as above gave a mixture containing (**10**) and carvone together with (**6**).

Reaction of cis-*Carveol with Chloroform and Base.*—(*a*) *cis*-Carveol (**19**) (6.0 g, 0.039 mmol), chloroform (14 g, 0.118 mol), and cetrimide (0.5 g) were stirred at 20 °C for 25 h with sodium hydroxide (10 g) in water (20 ml). The temperature was raised to 65 °C for 8 h and the products were then extracted between water (100 ml) and dichloromethane (100 ml). The aqueous layer was washed with dichloromethane (100 ml) and the combined organic layers were dried and the solvent was removed at 14 mmHg to give a brown oil. Distillation at 1.5 mmHg gave some unchanged starting material followed by a second fraction b.p. 128—135 °C which crystallised on standing (2.5 g). Recrystallisation of a portion (1.5 g) of the distillate gave 7,7-*dichloro*-4-*isopropenyl*-1-*methylbicyclo*[4.1.0]*heptan*-trans-2-*ol* (**21**) (450 mg) which was identical (n.m.r.) with a sample obtained above. Evaporation of the mother-liquor gave an oil which was a mixture of (**21**), starting material, and 4-(2,2-dichloro-1-methylcyclopropyl)-2-methylcyclohex-1-en-*cis*-3-ol (**22**) which was not separated at this stage. The residue showed only complex highfield signals in the ^1H n.m.r. spectrum.

(*b*) *Oxidation of the distillate.* The mother-liquor from distillation in (*a*) (1.1 g) was stirred with activated manganese dioxide (11 g) in carbon tetrachloride (50 ml). After 30 min the reaction was complete (n.m.r.); after filtration and removal of the solvent at 14 mmHg an oil remained which showed two fast-running and one slower-running spots on t.l.c. (silica, chloroform). Column chromatography gave a white crystalline solid identified as (**21**) (85 mg) corresponding to the slow-running spot. The fast-running spots did not separate from each other but were shown by n.m.r. and g.l.c. to be carvone and (**10**).

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