The Chemistry of Terpenes. Part 27.[1] The Halogenation of (+)-Thujone and of (−)-Carvotanacetone, and the Stereochemistry and Mechanism of Formation of 'Tribromothujone'

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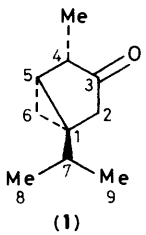
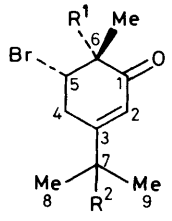
The gross structure and precise stereochemistry of 'tribromothujone' have been identified; its adjacent bromine atoms are *cis*-orientated. The mechanism of its formation is discussed. A number of halogenated compounds derived from (+)-thujone have been obtained and their absolute configurations determined. (−)-Carvotanacetone dibromide and two tribromides have been stereochemically identified.

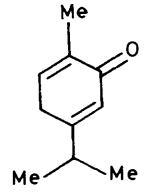
In 1893, O. Wallach[2] showed that when thujone (**1**)† in light petroleum is rapidly treated with an excess of bromine, a (±)-tribromo compound is formed. Later work[5] showed that 'tribromothujone' has the gross structure of (**2**), and a mechanism for its formation was suggested which involved the intermediate dienone (**3**). We have confirmed the gross structure of 'tribromothujone' and shown that one of its enantiomers has the absolute configuration of (**2**). However, we cannot accept the mechanism suggested[5] since the supposed intermediate (**3**) is the short-lived keto form of carvacrol (**4**), which brominates to give the 3,5-dibromo derivative (**5**).



(**1**)



(**2**) $R^1 = R^2 = Br$



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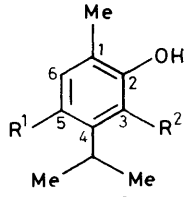
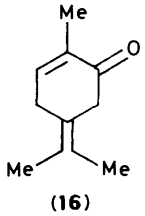
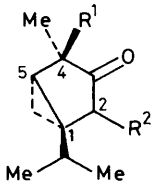


(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = R^2 = Br$
(**6**) $R^1 = H, R^2 = Br$
(**7**) $R^1 = Br, R^2 = H$

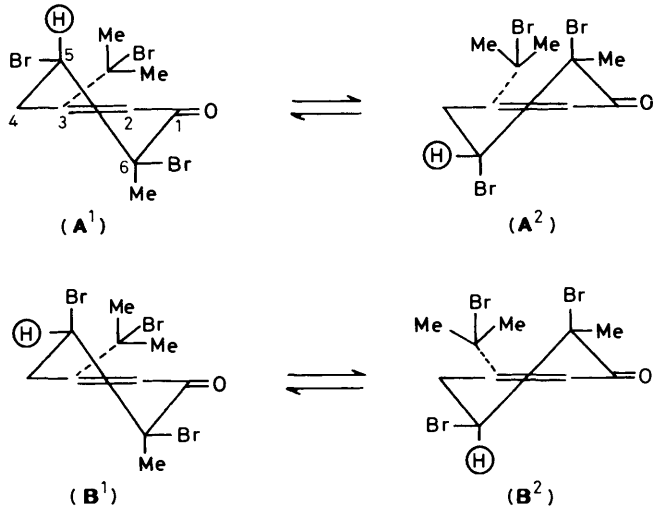


(**16**)



(**8**) $R^1 = Br, R^2 = H$
(**9**) $R^1 = Cl, R^2 = H$
(**10**) $R^1 = Br, R^2 = \beta\text{-}Br$
(**11**) $R^1 = Br, R^2 = \alpha\text{-}Br$
(**12**) $R^1 = Cl, R^2 = \beta\text{-}Br$
(**13**) $R^1 = Cl, R^2 = \alpha\text{-}Br$
(**14**) $R^1 = MeO, R^2 = H$
(**15**) $R^1 = Et_2N, R^2 = H$

† We use the nomenclature of S. P. Acharya *et al.*,[3] in which (+)-thujan-3-one has the *trans*-arrangement of the methyl and isopropyl groups. It has the absolute configuration[4] shown in (**1**), namely (+)-(1*S*,4*S*,5*R*)-thujan-3-one. For simplicity we name it (+)-thujone.



(**A**^{1}) (**A**^{2}) (**B**^{1}) (**B**^{2})

Figure 1.

Since starting our work we have seen P. de Mayo's[6] rejection of the mechanism mentioned above, for the same reason as the one we cite. He[6] suggested a mechanism involving intermediates having the gross structures of (**8**) and (**16**). We confirm the proposal that 4-bromothujone (**8**) is an intermediate in the formation of (**2**) and we demonstrate the absolute configuration shown, but as is shown in the sequel it is unlikely that (**16**) is involved in the reaction.

We first set out to confirm the gross structure of (**2**) and identify its stereochemistry. We have measured the optical rotation of (**2**) at several wavelengths and confirm that (**2**) is optically inactive; the mechanism of its formation must comply with this fact. The ^{13}C n.m.r. spectrum of (**2**) accords with its structure as does its ^1H n.m.r. spectrum. The configuration of 'tribromothujone' (**2**) is deduced as follows. There are two possible diastereoisomeric forms of (**2**) (see Figure 1), namely (**A**) and (**B**), and each has two possible half-chair conformations.

The 360 MHz ^1H n.m.r. spectrum of 'tribromothujone' shows very clearly that the 5-H(circled) is coupled (*J* 11 and 4.5 Hz) axially–axially and axially–equatorially. This fact rules out conformation (**A**^{2}) in which no axial couplings exist. Since, of the two conformers of (**A**), conformer (**A**^{1}) would be the less stable (Br, Br, and C=O are all flanking contiguously), it is already a strong argument in favour of configuration (**B**) for 'tribromothujone'. Of the two conformations of (**B**) only (**B**^{2}) has the required *trans*-diaxial arrangement of 5-H and 4β-H. In

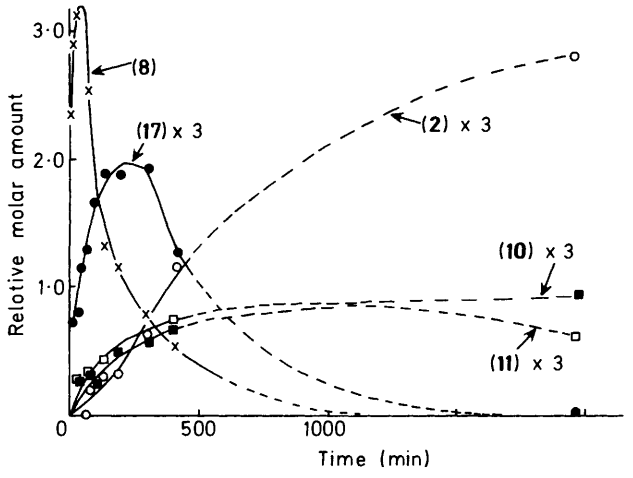


Figure 2. Relative molar concentration of intermediates and products in the early stages of the bromination of (+)-thujone in $CDCl_3$–CCl_4

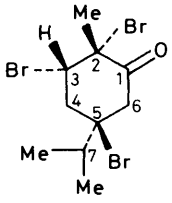
addition, ($\mathbf{B}^1$) would be less stable than ($\mathbf{B}^2$) since in the former the equatorial bromine atom at C-6 flanks the C=O group. Nuclear Overhauser (n.O.e.) difference spectra also support the assignment that ($\mathbf{B}^2$) represents the configuration and preferred conformation of the tribromide (**2**). Thus, saturation of the 6-methyl group gives a 10% enhancement of the nearby 5-axial proton signal. Since this 6-methyl signal is virtually coincident with the signal of one of the isopropyl methyl groups, there is also a 22% enhancement of the 4α-pseudoequatorial proton signal. This is unavoidable, but it is consistent with structure ($\mathbf{B}^2$). It is, therefore, clear that the tribromide is (±)-*cis*-5,6-dibromo-3-(1-bromo-1-methylethyl)-6-methylcyclohex-2-enone (**2**).

Under less vigorous conditions than those employed,[2] (+)-thujone can be monobrominated to give (−)-(1*S*,4*R*,5*S*)-4-bromothujan-3-one (**8**). This is an unstable compound which slowly loses hydrogen bromide to yield carvacrol (**4**), but its formation can be followed in solution by ^{1}H n.m.r. spectroscopy. Initially slow, enolisation of thujone accelerates, and bromination is complete in a few minutes in dilute $CDCl_3$ solution in the presence of 1 mol equiv. of bromine (see Experimental section). The ^{1}H n.m.r. spectrum of (**8**) can be unambiguously assigned and compares closely with that of the more stable (−)-4-chlorothujone (**9**) described in the sequel. Signals of (**8**) (see Experimental section) were similar to those of (+)-thujone (**1**) except for the absence of the 4-methyl doublet and 4-H multiplet and their replacement by a 3-H singlet at δ 1.74. The assignments were confirmed by the spin-decoupling experiments described and the stereostructure was deduced from a n.O.e. difference spectrum which showed a 5.3% enhancement of the 6α-H signal on saturation of the 4-Me group. This is consistent only with an α-methyl configuration.

The decomposition of 4-bromothujone (**8**) in $CDCl_3$ was also monitored by ^{1}H n.m.r. spectroscopy. At room temperature, carvacrol (12%) was formed in 4 days and this rose to *ca.* 60% in 20 days. Complete decomposition took place in *ca.* 60 days, but decomposition of solvent-free 4-bromothujone took place in a matter of minutes; it began immediately solvent was removed.

It was clear, at this stage, that 4-bromothujone (**8**) was likely to be an intermediate in the formation of 'tribromothujone' (**2**). With a view to determining the nature of other intermediates we carried out the bromination of (+)-thujone (**1**) with an excess of bromine under controlled conditions, and the products were monitored by n.m.r. A solution of (+)-thujone (4.40% in $CDCl_3$; 0.104 ml) was treated at 20 °C with a solution of bromine (12.5% in CCl_4; 0.18 ml) to which $CDCl_3$ (0.25 ml) was added. Measurements were made by integration of uniquely assignable signals against the chloroform peak. The accuracy of this technique is limited, but repeated experiments showed consistent results. Under these conditions, the rate of formation of 4-bromothujone was too rapid to measure in the very early stages. Figure 2 shows the results obtained.

Figure 2 shows clearly that as 4-bromothujone (**8**) decomposes, 'tribromothujone' (**2**) is formed. However, a new compound, whose ^{1}H n.m.r. spectrum (discussed below) corresponds to that expected of 2,3,5-tribromo-5-isopropyl-2-methylcyclohexanone (**17**) is formed as 4-bromothujone decays. In turn the tribromo compound (**17**) decays as 'tribromothujone' (**2**) is formed. The figure also shows that the dibromothujones

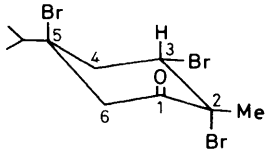


(**17**)

(**10**) and (**11**) are likely to be formed by a slower competing reaction and are unlikely intermediates in the formation of 'tribromothujone' (**2**). The structures of these dibromo compounds were assigned by reference to the very similar ^{1}H n.m.r. spectra of the bromochorothujones (**12**) and (**13**) (see below) which have greater stability than their bromo analogues.

Most significant was the rise and fall in concentration of the compound (**17**). By spectroscopic studies approximately 4 h after mixing the thujone and bromine, when the concentration of the tribromo intermediate was at its maximum, it was possible to determine its structure almost completely. The expected signals and spin–spin couplings were observed (see Experimental section) for all the protons although a few were partially obscured by signals from other components in the reaction mixture, which became steadily more complex. The assignments and spin–spin couplings between all of the 3,4α and 4β, and 6α and 6β protons were confirmed by interrelated spin–decoupling experiments; likewise the signals of the spin-isolated unsubstituted isopropyl group were shown to follow closely the same intensity/time profile as those of the cyclohexane ring. The most easily recognised signal of this intermediate was the sharp doublet at δ 3.69 (*J* 15 Hz) due to the 6α-proton; this signal, which proved the absence of a 5-H atom, was used to measure the concentration of (**17**) relative to $CHCl_3$. The 3β-H could be clearly seen, although overlapping with other signals, as a sharp double doublet (*J* 11, 4.5 Hz) at δ 4.48 revealing an equatorial 3-Br substituent. The chemical shift of this proton is deshielded relative to that in (2*R*,3*S*,5*S*,6*S*)-2,3,6-tribromo-5-isopropyl-2-methylcyclohexanone (**27**) (see below) and this can be explained by the presence of a β-axial Br substituent at C-5 in (**17**). Attempts to assign the stereostructure at C-2 by a n.O.e. difference spectrum of (**17**) on saturation of the 2-Me group gave a modest enhancement of the 3β-axial H signal (≈5%) which suggested the 2α-axial bromine configuration.

We, therefore, propose the full stereostructure (**17a**) for this



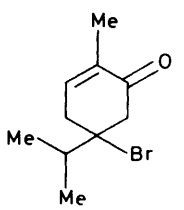
(**17a**)

significant component of the bromination mixture. Although this (**17**) was only one of several components present in the middle stages of the reaction it was, through ^{1}H n.m.r., the most easily recognised and major of the components which were not final products. Its quantitative relationship to the decline of the bromothujone (**8**) and to the build up of the product (**2**), as well as its identical stereochemistry at C-2 and C-3 to C-5 and C-6 in (**2**) made it a most likely intermediate between these components.

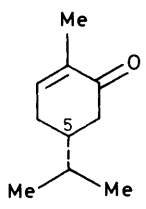
Bromination of (+)-thujone in $CDCl_3$ under controlled conditions using only 1.0 mol equiv. of bromine showed that 4-bromothujone (**8**) was the sole product, whilst treatment with further quantities (2.0 mol equiv.) of bromine led to a considerable reduction in the amount of 4-bromothujone and the formation of 'tribromothujone'. The dibromo compounds (**10**) and (**11**) were formed in small quantities and also a minor amount of 3,5-dibromocarvacrol (**5**). These experiments clearly show that 4-bromothujone (**8**) is the primary intermediate in the formation of 'tribromothujone' (**2**). That the dibromo compounds (**10**) and (**11**) are formed by a competing side reaction is supported by the fact that the corresponding bromochlorothujones (**12**) and (**13**) are formed only slowly from 4-chlorothujone (**9**).

The course of the bromination of thujone to 'tribromothujone' may be proposed in outline as follows. We envisage as a key stage after the formation of the monobromo compound (**8**), opening of the cyclopropane ring in which bromide takes a part. In the sequel we have demonstrated that such a reaction takes place with zinc bromide on the chlorothujones (**12**) and (**13**). This step would be expected to lead to an α,β-unsaturated bromo ketone (**18**). Such an intermediate would be very short lived—but in the presence of an excess of bromine, it would rapidly brominate to give a tribromide of the *gross* structure of (**17**). Similar rapid bromination has been demonstrated (see below) for both carvotanacetone (**19**) and carvenone (**31**). Finally, the tribromide (**17**), on loss of hydrogen bromide, would afford an α,β-unsaturated ketone of the gross structure of (**21**) which on further bromination *via* its dienol [or possibly by a free radical mechanism: see (**13**) ⟶ (**20**) below] would lead to 'tribromothujone' (**2**). This last step implies that addition to the double bond in (**21**) is precluded or impeded.

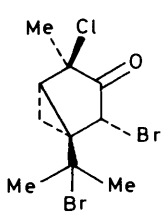
Although we have been unable to resolve the tribromide (**2**) on chiral columns, its lack of optical activity almost certainly indicates a racemate. This stereochemical result may be tentatively explained. Models show that attack of bromide at C-1 with loss of bromide at C-4 can occur on the α or β face of the bromothujone (**8**) to give either or both enantiomers of (**18**), but with a greater possibility of attack at the β face.



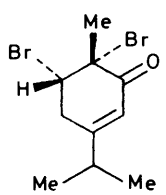
(**18**)



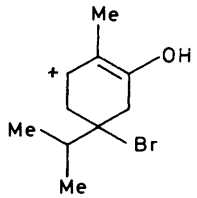
(**19**)



(**20**)



(**21**)



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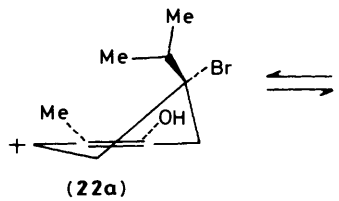
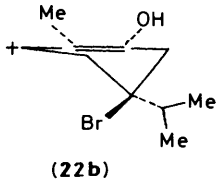
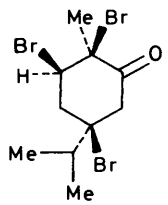


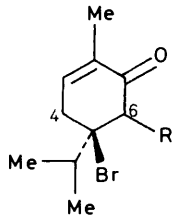
(**22a**)



(**22b**)



(**23**)



(**24**) R = β - Br

(**25**) R = α - Br

α,β-Unsaturated ketones are known to undergo bromination by a mechanism[7] involving the protonation of the keto group, followed (*a*) by attack of bromide at the β-carbocation and (**b**) by electrophilic bromination of the β-bromo enol. If we apply this to *either* enantiomer of (**18**) we find that the derived carbocation (**22**) can exist in two reasonable conformations, *e.g.* for the *S* form, (**22a**) and (**22b**) which each present a single, planar, unhindered face.

Models suggest that attack of bromide will be equally facile and probable on the α-face of (**22a**) and the β-face of (**22b**). This would lead to two possible *cis*-2,3-dibromo diastereoisomeric forms (**17**) and (**23**) in equal amounts which, on *complete* loss of hydrogen bromide from C(5)–C(6) in each would give racemic (**21**).

The observation of one predominant diastereoisomeric form of (**17**) of the tribromide by n.m.r. analysis in the bromination mixture may be explained by difference in the rate of loss of hydrogen bromide from (**17**) and (**23**); presumably the relatively stable conformation of (**17**) gives it a longer lifetime.

An alternative, simpler explanation for the formation of *racemic* (**18**) and hence (**21**) and (**2**) envisages the acid-catalysed loss of bromide from C-4 of the bromothujone (**8**) giving a planar classical carbocation [(**19**) with the charge localised at C-5] followed by attack of bromide. A 'triangular' non-classical carbocation (*cf.* ref. 8) may initially be formed but direct discharge of this by bromide at C-5 would be expected to be stereoselective or stereospecific.[8]

In the early stages of our work, we turned from the bromination to the chlorination of (+)-thujone, because of the instability of 4-bromothujone. Chlorination of (+)-thujone can be conveniently performed with sulphuryl chloride yielding (−)-(1*S*,4*R*,5*S*)-4-chlorothujan-3-one (**9**) which is much more stable than its bromo analogue, but it yields carvacrol with time. Its ^{1}H n.m.r. spectrum (see Experimental section) is similar to that of (**8**). A n.O.e. difference spectrum of (**9**) shows, on saturation of the 4-Me group, a 4% enhancement of the 6α-H signal which agrees with the *cis*-arrangement of this proton and the 4α-methyl group. In fact, both bromination and chlorination of thujone is stereospecific, the attack of halogen on its 3,4-enol being on the opposite side of the molecule to the three-membered ring.

(−)-4-Chlorothujone (**9**) is slowly solvolysed in cold methanol, and rapidly under reflux, yielding carvacrol (**4**) and its methyl ether. The initially formed carbocation (at C-4) rearranges, with opening of the 3-membered ring giving a carbocation at C-1 (thujone numbering) which loses a proton

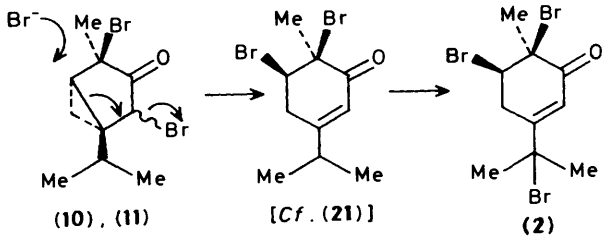


Figure 3.

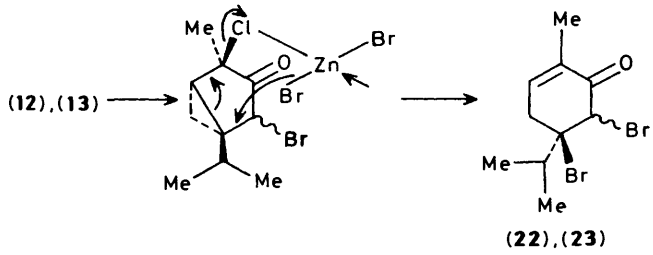


Figure 4.

giving carvacrol *via* the dienone (**3**). We have seen no evidence of the formation of the dienone (**16**) (*cf.* ref. 6) which would be formed by loss of a proton from C-7. Treatment of the chloro ketone (**9**) with cold methanolic sodium methoxide rapidly and stereospecifically affords (−)-(1*S*,4*R*,5*S*)-4-methoxythujan-3-one (**14**) by β-face attack of methoxide on the C-4 carbocation. The chloro ketone (**9**) reacts with diethylamine in methanol giving a mixture of the ether (**14**) and (−)-(1*S*,4*R*,5*S*)-4-diethylaminothujan-3-one (**15**), but with chloroform as solvent the amine (**15**) is the sole product. In the latter case, an excess of diethylamine evidently acts as a ionizing solvent. A solution of diethylamine in methanol presumably contains the base $MeO^{-}NH_2^{+}Et_2$.

The ^{1}H n.m.r. spectra of the methyl ether (**14**) and the amine, (−)-(1*S*,4*R*,5*S*)-4-diethylaminothujan-3-one (**15**) are fully in accord with their structures and n.O.e. enhancements confirm the configuration of the 4-methyl group.

Mono-bromination of (−)-4-chlorothujone (**9**) is slow giving a mixture of (−)-(1*S*,2*S*,4*R*,5*S*)-2-bromo-4-chlorothujan-3-one (**12**), a solid, and its 2-epimer (−)-(1*S*,2*R*,4*R*,5*S*)-2-bromo-4-chlorothujan-3-one (**13**), a liquid, in the proportion of *ca.* 3:2. The i.r. spectrum of (**13**) showed carbonyl absorption at the high value of 1 774 cm^{-1}. The corresponding absorption of (**12**) was at 1 765 cm^{-1} and differed little from that of (−)-4-chlorothujone (**9**). In all these compounds the effect of the halogens on the C=O absorption was particularly marked. The ^{1}H n.m.r. spectra of these bromo chloro compounds confirmed their structures. Thus for (**12**) the cyclopropyl H signals appear as multiplets at δ 2.16 (5-H), −0.08 (6α-H), and 1.10 (6β-H) with the expected couplings. The 2α-H signal appeared as a very sharp singlet at δ 4.21. In the epimer (**13**), apart from significant chemical-shift differences for the 6α and isopropyl protons, the 2β-H signal was a doublet (*J* 1.5 Hz) at δ 5.35 due to W coupling with the 6β-H. The configuration of (**12**) was confirmed by *X*-ray measurements kindly performed by Dr. C. Cardin of Trinity College. The slow bromination of 4-chlorothujone (**9**) is an indication of the strain produced in the molecule in the formation of its 2,3-enol; significantly no cyclopropyl ring opening took place.

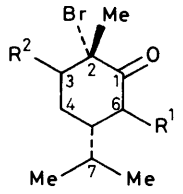
It will be noticed that on monobromination of 4-chlorothujone (**9**) the 2β-bromo-4-chlorothujone (**12**) is formed in larger quantity than its 2-epimer (**13**). A model of the 2,3-enol of (**9**) shows that the β-side of the molecule is the less hindered, thus favouring the faster formation of (**12**). However, when (**12**) was stirred with pyridinium bromide in dimethyl sulphoxide, it was equilibrated with its epimer (**13**) giving a mixture containing *ca.* 75% of the latter (based on ^{1}H n.m.r. spectra and optical rotation of the mixture). A model of (**12**) shows that the two halogen atoms are in a quasi-diaxial relationship. Thus, on bromination of 4-chlorothujone, (**12**) is kinetically favoured, but its epimer (**13**) is the more thermodynamically stable.

As part of the investigation of the bromination of the chlorothujone (**9**), it was shown that the bromochlorothujone (**13**) underwent further smooth bromination in $CDCl_3$–CCl_4 in laboratory light; no bromination takes place in the dark. During 2.5 h, 50% of the starting material was converted into the 7-bromo derivative (**20**) and the product was ultimately almost pure (1*S*,2*R*,4*R*,5*S*)-2,7-dibromo-4-chlorothujone (**20**) as judged by n.m.r. spectroscopy. In its spectrum (**20**) lacks the 7-H multiplet of its precursor (**13**) and the 8- and 9-methyl groups of (**20**) appear as singlets. The apparently free-radical bromination of (**13**) at C-7 presents, at first sight, an analogy for the bromination of the dibromide (**21**) to 'tribromothujone' (**2**). The ionic electrophilic bromination of the dienol of (**21**) is, however, much more likely; the relatively slow free-radical reaction and the variable presence of light is not consistent with the evidently very rapid bromination of (**21**) as judged by our inability to observe the latter in solution.

At an early stage in our investigations, we found it attractive to think that the dibromothujones (**10**) and (**11**) could yield the unsaturated ketone of the gross structure of (**21**) by reaction with bromide. The reaction envisaged is shown in Figure 3. This reaction would be expected to be concerted, the bromide ion attacking C-5 on the upper face of the molecule. The 2α-bromo ketone (**11**) would be expected to react more rapidly than its epimer (**10**). With these considerations in mind, we treated the corresponding bromo chloro ketones (**12**) and (**13**) with zinc bromide in ether. As expected, the 2β-bromo chloro ketone (**12**) reacted very slowly, taking *ca.* 40 h for near-completion while its epimer (**13**) was completely consumed in 5 h. However, the products from the two reactions were not identical. In fact the 2β-bromo chloro ketone (**12**) gave a mixture of (−)-(5*R*,6*R*)-5,6-dibromo-5-isopropyl-2-methylcyclohex-2-enone (**24**) and 3-bromocarvacrol (**6**) in the proportions of *ca.* 2.3:1 (^{1}H n.m.r.). The 2α-bromo chloro ketone (**13**) afforded a mixture of (+)-(5*R*,6*S*)-5,6-dibromo-5-isopropyl-2-methylcyclohex-2-enone (**25**) and possibly some of its epimer. It was thus the C-4 tertiary halogen which was expelled in the reactions, a not unlikely result. In the light of this, it seemed clear that the dibromothujones (**10**) and (**11**) would lose their tertiary bromine atoms even more readily than the chlorine atoms of (**12**) and (**13**).

We assign the configurations at C-5 of the dibromo ketones (**24**) and (**25**) on the expectation that substitution proceeds intramolecularly *via* a metal complex as shown in Figure 4. Such six-membered transition states are well known[9] and would result in a *syn*-facial S_N2' type displacement of chloride.

A further point of interest is that throughout the course of the monitored reaction of zinc bromide with the bromo chloro ketone (**12**) the relative quantities of dibromo ketone (**24**) and 3-bromocarvacrol (**6**) remained approximately constant, thus suggesting that the dibromo ketone (**24**) is not the precursor of 3-bromocarvacrol. However, an attempt to purify the dibromo ketone (**24**) by vacuum distillation afforded 3-bromocarvacrol; similarly, loss of hydrogen bromide takes place on chromatography on silica. We have thus not been able to obtain a pure specimen of (**24**) but on the basis of the specific rotation of its mixture with 3-bromocarvacrol, it appears to be laevorotatory, with $[\alpha]_D^{20}$ of the order of −3°. Its readiness to lose hydrogen bromide is associated with the favourable geometry at C-5 and C-6. The solid unsaturated dibromo ketone (**25**) shows $\lambda_{max.}$(EtOH) 245 nm (log ε 3.2) and $\nu_{max.}$(Nujol) 1 690 and 1 650

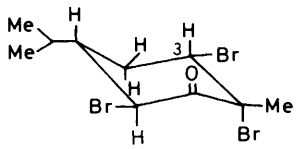


(**26**) R^1 = H, R^2 = Br

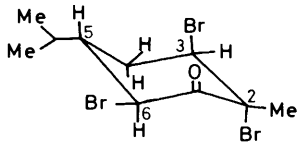
(**27**) R^1 = β-Br, R^2 = α-Br

(**28**) R^1 = R^2 = β-Br

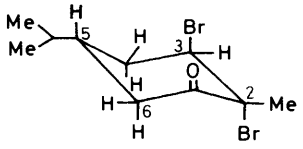
(**29**) R^1 = H, R^2 = β-Br



(**27a**)



(**28a**)



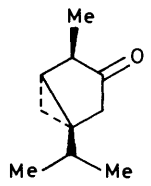
(**29a**)

cm^{-1} in agreement with its structure. Its ^{1}H n.m.r. spectrum shows the expected vinyl methyl group as a multiplet $J_{10,4\alpha}$ 2.5 Hz, $J_{10,4\beta}$ 1.5 Hz) at δ 1.90, olefinic H multiplet at δ 6.55, and a singlet at δ 4.47 for the 6β-H.

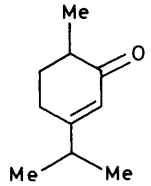
As an analogy for the intervention of the α,β-unsaturated ketone (**18**) as an intermediate in the formation of 'tribromothujone' (**2**) we investigated the bromination of (−)-carvotanacetone (**19**). It was of particular interest that 'tribromothujone' (**2**) and the intermediate (**17**) both have a *cis*-1,2-dibromo configuration. Wallach[10] obtained a liquid dibromide from carvotanacetone (**19**) to which he gave the gross structure of (**26**). Following Wallach, we used acetic acid as solvent but employed 2 mol equiv. of bromine. The first mol equiv. was consumed rapidly and the second, slowly. Two solid products were isolated, namely (−)-(2*R*,3*S*,5*S*,6*S*)-2,3,6-tribromo-5-isopropyl-2-methylcyclohexanone (**27**), a 2,3-*cis*-dibromide and its 3-epimer (+)-(2*R*,3*R*,5*S*,6*S*)-2,3,6-tribromo-5-isopropyl-2-methylcyclohexanone (**28**). Both compounds showed strong maxima at 1 740 cm^{-1} characteristic of α-bromocyclohexanones. Their configurations are assigned on the basis of their ^{1}H n.m.r. spectra. For (**27**), the 3-H signal was a double doublet at δ 3.82 with *J* 12 and 5 Hz indicating an axial configuration. The 6-H gave a doublet, *J* 13 Hz at δ 5.52 assignable only to a diaxially coupled proton, and this, together with the known α-isopropyl configuration of the starting carvotanacetone fixed the relative configurations at C-3, C-5, and C-6 as shown in (**27a**). These assignments were confirmed by spin decoupling experiments, and an n.O.e. difference spectrum, on saturation of the 2-methyl group, gave a 9.6% enhancement of the 3-H signal but had no effect on the 6-H signal. These results were in keeping with an equatorial 2β-methyl group. For the 3-epimer (**28**), the significant difference was that the 3-H signal was a triplet, *J* 3 Hz at δ 4.78, as expected for the equatorial 3α-H and the 5-H signal was at considerably lower field (δ 2.58) compared with (**27**) (δ 1.79) due to the (additional) 3,5-diaxial H, Br relationship in (**28a**).

A further product from this bromination reaction was 5-bromocarvacrol (**7**).

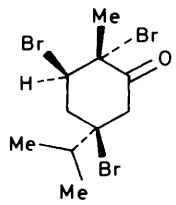
When (−)-carvotanacetone (**19**) was treated with 1 mol equiv. (*cf.* ref. 10) of bromine it rapidly gave (+)-(2*R*,3*R*,5*S*)-2,3-dibromo-5-isopropyl-2-methylcyclohexanone (**29**). Its ^{1}H n.m.r. spectrum showed large diaxial couplings (12 Hz) for its 4α- and 6α-protons. This fact, together with the 5α-isopropyl group (*R*-configuration) present in (−)-carvotanacetone itself, leads only to the conformer (**29a**). Its 3α-H signal at δ 4.80 was a triplet (*J* 3 Hz) showing *e,a* and *e,e* couplings to the 4α- and 4β-protons respectively, thus proving that the 3-bromine atom must be β-orientated. On saturation of the 2-methyl group, an n.O.e. difference spectrum showed a 6% enhancement of the 3α-proton as the only measurable effect. This is consistent with 2β-methyl group. An α-configuration for this group would be expected to give a significant enhancement of both the 4α- and 6α-proton signals.



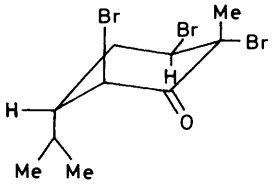
(**30**)



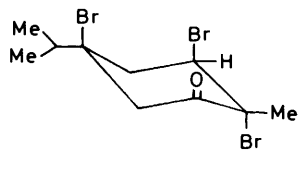
(**31**)



(**32**)



(**28b**)



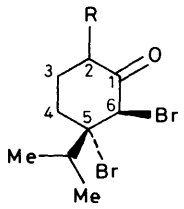
(**32a**)

Monitoring by n.m.r. of the bromination of (−)-carvotanacetone in trideuterioacetic acid, but using more dilute solutions than those in the preparative experiments also confirmed that initially the *trans*-dibromide (**29**) is formed at a rapid rate. With further addition of bromine, this was slowly converted into the tribromide (**28**) which, after several days, was partially (*ca.* 50%) converted into its 3-epimer (**27**), although other products were also present at this stage.

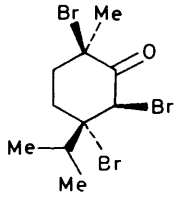
The direction of attack of bromide on the C-3 carbocation formed when (−)-carvotanacetone (**19**) is protonated will be dictated by the α-orientated isopropyl group. Thus β-face bromination will be expected to predominate. The next bromine atom will enter axially at C-2-giving the *trans*-dibromide (**29**). The 2α-axial bromine of (**29**) will influence the direction of attack of bromine at C-6, *i.e.* on the β-face of the molecule. The tribromo compound (**28**) will thus result. The more likely of the two reasonable conformers of (**28**) is (**28a**). In the alternative (**28b**) there is considerable 1,3-diaxial interaction between the 2-methyl group and the 6-bromine atom, as well as an unfavourable 2,3-dibromo keto interaction.

However, in (**28a**) the 3-bromine is both axial and has an unfavourable interaction with the C=O group. It is reasonable to assume that the 3-bromine will be displaced by bromide entering from the opposite side thus yielding the *cis*-dibromide (**27**) in which the 3-bromine is equatorially disposed. The carbonyl group with its incipient cation at C-1 will probably oppose the formation of a cation at C-2 and thus resist epimerisation there. In fact, both preparatively and as shown by n.m.r., both (**27**) and (**28**) are eventually formed in the bromination of (−)-carvotanacetone.

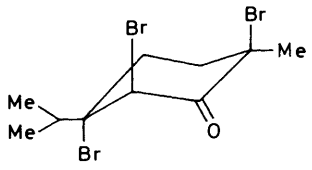
These results appear relevant to the *cis*-5,6 and -2,3 dibromo configurations of 'tribromothujone' (**2**) and the intermediate (**17**). In the case of the bromination of the intermediate (**18**), initial *trans* addition to the double bond would give isomers of



(33) R = β Me
(34) R = α Me



(35)



(35a)

(17), *e.g.* (32), in which, even for the more stable conformer (32a), the 3-axial bromine substituent would suffer an additional 1,3-diaxial interaction with 5-bromine: epimerisation at C-3 would, therefore, be expected to occur readily. As with carvotanacetone, bromination of (±)-carvenone (31) can be followed by ^{1}H n.m.r. analysis. Even under dilute conditions it is initially very rapid. Within 4 min, when the first spectrum was taken, all the starting material was converted into a mixture of diastereoisomeric dibromides as can be seen from the replacement of the olefinic signal of (31) by a multiplet signal at δ 4.63 (COCHBr). By analogy with the product of initial bromination of carvotanacetone (19), from their ^{1}H n.m.r. spectra and from their further bromination to the tribromide (35) (see below) these initial products are assigned the racemic structures of (33) and (34). In the presence of an excess of bromine, this mixture brominates further and after 2—3 h the expected bromination at C-2 of (33), (34) leads to a virtually pure single diastereoisomeric tribromide, as can be seen from clean signals at δ 1.95 (s, CBrMe), 1.06 and 1.15 (2d, *J* 7 Hz, $CHMe_2$), and 4.72 (d, *J* 2.5 Hz, CHBr). The detailed features of the ^{1}H n.m.r. spectrum of this tribromide (see Experimental section) which slowly transformed in the presence of an excess of bromine to other products, identify it is as the racemate of structure (35) and conformation (35a). We made no attempt to isolate the solvent-free samples of the polybromides (33), (34), and (35).

An attempt to effect a skeletal rearrangement[11] of (−)-2-β-bromo-4-chlorothujone (12) by refluxing in dioxane with zinc gave a mixture of (+)-thujone and (−)-isothujone (30) (86:14) and carvacrol (4).

Experimental

Optical rotations were measured in chloroform, and unless otherwise mentioned, n.m.r. measurements were made in deuteriochloroform at 360 MHz (^{1}H) and 90.56 MHz (^{13}C) on a Bruker W.M. 360 instrument, and i.r. measurements as either liquid films (L) or Nujol mulls (N). (+)-Thujone (1) was used since it could be obtained both chemically and optically pure.

(+)-(1S,4S,5R)-*Thujan*-3-*one* [(+)-*Thujone*)] (1), ex-*Oil of* Artemisia kurramensis.—The crude oil (kindly supplied by Messrs. T. and H. Smith of Edinburgh) was treated as described earlier[12] and the fraction containing (+)-thujone and (−)-isothujone (30), b.p. 92—103 °C at 27—28 mmHg was collected. This oil (50 g) was left overnight with sodium methoxide in methanol (2%; 250 ml) (*cf.* ref. 3). Work-up gave a product $[\alpha]_D^{20}$ +34.3° (*c* 2.4); *ca.* 59% of (+)-thujone. The equilibrated oil (60 g) in ethanol (36 ml) was added to an aqueous solution of sodium metabisulphite to which sodium hydrogen carbonate has been added to remove the odour of sulphur dioxide (sodium metabisulphite, 75 g in a 130 ml solution), and the mixture was rapidly stirred for 24 h. The sparingly soluble bisulphite compound of (+)-thujone was collected, washed with ether until free from oil, suspended in water (100 ml), covered with a layer of ether (50 ml), and rapidly stirred; solid sodium carbonate was then added in portions until all the bisulphite compound had disappeared and the aqueous layer was alkaline to phenolphthalein. The ether layer was removed and the aqueous layer was again extracted with ether (2 × 50 ml). The combined extracts yielded (+)-thujone (1) (14.3 g), b.p. 76 °C at 20 mmHg, $[\alpha]_D^{20}$ +82.1° (*c* 1.35)* The unchanged oil was added to the filtrate from the bisulphite adduct, solid sodium metabisulphite (5 g) was added and the solution was stirred for 24 h. Work-up as before yielded more (+)-thujone (5 g), $[\alpha]_D^{20}$ +81.8° (*c* 1.1). More (+)-thujone was obtained by equilibrating the unchanged oil with methoxide and proceeding as described. The process can be repeated. In all, (+)-thujone (30 g) of highest quality was obtained. It gave δ_H −0.04 (1 H, dd, *J* 6, 4 Hz, 6α-H), 0.60 (1 H, ddd, *J* 8.5, 6, 2 Hz, 6β-H), 0.93 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 1.01 (3 H, d, *J* 6.5 Hz, 9- or 8-Me), 1.04 (3 H, d, *J* 6.5 Hz, 10-Me), 1.45 (2 H, overlapping m, 5 H, and hept., *J* 6.5 Hz, 7-H), 2.13 (1 H, d, *J* 18 Hz, 2α-H), 2.55 (1 H, dt, *J* 18, 2 Hz, 2β-H), and 2.72 (1 H, q, *J* 6.5 Hz, 4-H). Irradiation of the dt at δ 2.55 (2β-H), collapsed the d at 2.13 (2α-H) to a s, and the m at δ 0.60 (6β-H) to a br t. Irradiation of the q at δ 2.72 (4-H) collapsed the d at δ 1.04 (10-Me) to a s and simplifed the obscured m at δ 1.45 (7-H). Irradiation of the m at δ 0.60 (6β-H) collapsed the dt at δ 2.55 (2β-H) to a dd and the m at δ −0.04 to a br d.

(±)-cis-5,6-*Dibromo*-3-(1-*bromo*-1-*methylethyl*)-6-*methylcyclohex*-2-*enone* ('*Tribromothujone*') (2).[2,5]—Using Wallach's conditions,[2] (+)-thujone (0.5 g) gave the tribromo compound (2) (0.2 g), m.p. 122 °C (decomp.), $[\alpha]_D^{20}$ 0°; $\nu_{max.}$(N) 1 687 and 1 621 cm^{-1}; δ_C 26.0 (q, 10-Me), 31.8 and 32.0 (2 q, 8-, 9-C), 37.7 (t, 4-C), 55.1 (d, 5-C), 61.9 (s, 7-C), 66.3 (s, 6-C), 119.9 (d, 2-C), 162.9 (s, 3-C), and 189.2 (s, 1-C); δ_H 1.94 (3 H, s, Me), 2.03 (3 H, s, Me), 2.04 (3 H, s, Me), 3.17 (1 H, ddd, J_{gem} 17 Hz, $J_{4a,5a}$ 11 Hz, $J_{4a,2}$ 2.6 Hz, 4α-H), 3.36 (1 H, dd, J_{gem} 17 Hz, $J_{4e,5a}$ 4.5 Hz, 4β-H), 4.08 (1 H, dd, $J_{5a,4a}$ 11 Hz, $J_{5a,4e}$ 4.5 Hz, 5-H), and 6.18 (1 H, d, $J_{2,4a}$ 2.6 Hz, 2-H). N.O.e. difference spectra show that saturation of the two Me groups at δ 2.03 and 2.04 gave a 10% enhancement of the 5-axial H signal, a 22% enhancement of the olefinic 2 H, and a 4% enhancement of the 4β-equatorial H signals: *m/z* 311 (M^+ − Br, 52%), 309 (M^+ − Br, 100), 307 (M^+ − Br, 54), 230 (M^+ − Br_2, 27), and 228 (M^+ − Br_2, 26) (Found: *M*, 389.8471 and 387.8504. Calc. for $C_{10}H_{13}{}^{81}Br_2{}^{79}BrO$: *M*, 389.8475; $C_{10}H_{13}{}^{79}Br_2{}^{81}BrO$; *M*, 387.8495. Found: C, 31.1; H, 3.3. Calc. for $C_{10}H_{13}Br_3O$: C, 30.9; H, 3.4%).

Monobromination of (+)-*Thujone*. (−)-(1S,4R,5S)-4-*Bromothujan*-3-*one* (8).—In a typical experiment, (+)-thujone (4.7 mg) in $CDCl_3$ (0.5 ml) was treated with an excess (*ca.* 1.3 mol equiv.) of bromine in CCl_4 (0.04 ml) and ^{1}H n.m.r. spectra were obtained at 2-min intervals. The relative molar amounts of (+)-thujone and monobromothujone (8) were calculated by simple integration, thus:

Time (min)	% Product (8)
2	14
4	25
6	45
8	80
10	100

* Ref. 13 gives $[\alpha]_D$ +78.8° (neat).

The monobromo compound (**8**), which was relatively stable in solution, gave δ_H 0.07 (1 H, dd, *J* 7, 3.5 Hz, 6α-H), 0.80 (1 H, ddd, *J* 8.5, 7, 3 Hz, 6β-H), 0.97 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 1.08 (3 H, d, 9- or 8-Me), 1.44 (1 H, hept., *J* 6.5 Hz, 7-H), 1.74 (3 H, s, 10-Me), 1.95 (1 H, dd, *J* 8.5, 3.5 Hz, 5-H), 2.15 (1 H, d, *J* 17 Hz, 2α-H), and 3.08 (1 H, dd, *J* 17, 3 Hz, 2β-H). Irradiation of the m at 0.07 (6α-H) collapsed the m at 0.80 (6β-H) to a dd and the dd at 1.95 (5-H) to a d. Irradiation of the dd at 3.08 (2β-H) collapsed the d at 2.15 (2α-H) to a s and the m at 0.80 (6β-H) to a dd. Irradiation of the hept. at 1.44 (7-H) collapsed each of the two d at 0.97 and 1.08 (8- and 9-Me) to a s. An n.O.e. difference spectrum showed a 5.3% enhancement of the 6α-H signal on saturation of the 10-Me group.

After 16 days the bromo compound (**8**) was largely (n.m.r.) converted into carvacrol (**4**).

Bromination of (+)-Thujone (**1**) *with an Excess of Bromine in Deuteriochloroform: Kinetic Observation of the Intermediate* (**17**).—A solution of (+)-thujone [(22.2 mg) in deuteriochloroform (0.5 ml)] (0.104 ml) was diluted with deuteriochloroform (0.25 ml) and a solution of bromine [(1.0 ml) in carbon tetrachloride (25 ml)] (0.18 ml) was added. The solution was kept at 20 °C and monitored by 360 MHz ^{1}H n.m.r. spectroscopy. Within the first 10 min the thujone was almost completely converted into (1*S*,4*R*,5*S*)-4-bromothujan-3-one (**8**) and this decayed with the gradual build up of less than equimolar proportions of 'tribromothujone' (**2**) and the dibromothujones (**10**) and (**11**). These three products were unambiguously identified from the authentic compound (**2**) and by very close analogy [for (**10**) and (**11**)] with the more stable chloro analogues (**12**) and (**13**). In the early stages of the reaction, however, the build-up and decay of a fourth component (**17**) could be observed which reached a maximal concentration under these conditions after about 2 h. The approximate relative molar concentrations were obtained by integration of suitable signals relative to the chloroform peak (see Figure 2). The component (**17**) was amenable to detailed spectroscopic examination at its maximal concentration and showed δ_H 1.09 (3 H, d, *J* 7 Hz, 8- or 9-Me), 1.12 (3 H, d, *J* 7 Hz, 9- or 8-Me), 1.88 (1 H, d, *J* 7 Hz, 7-H), 2.0 (s, 2 Me), 2.54 (1 H, dd, *J* 13.5, 11.5 Hz, 4α-H), 2.74 (1 H, d, br, *J* 13.5 Hz, 4β-H), 3.00 (1 H, dd, *J* 15, 2 Hz, 6β-H), 3.69 (1 H, d, *J* 15 Hz, 6α-H), and 4.48 (1 H, dd, *J* 11, 4.5 Hz, 3β-H). Irradiation of the dd at δ 3.69 (6α-H) collapsed the dd at 3.00 (6β-H) to a d. Irradiation of the dd at 2.54 (4α-H) collapsed the broad d at 2.74 (4β-H) to a broad s and the broad dd at 4.48 (3β-H) to a dd, *J* 4.5 Hz and just visible 2 Hz. Irradiation of the broad d at 2.74 (4β-H) collapsed the dd at 3.0 (6β-H) and 4.48 (3β-H) each to doublets. Finally, irradiation of the 7-H at δ 1.88 collapsed the two d at 1.09 and 1.12 (8- and 9-Me) each to a s.

Monochlorination of (+)-Thujone: (−)-(1S,4R,5S)-4-*Chlorothujan*-3-*one* (**9**).—Freshly distilled sulphuryl chloride (3 g) in dry carbon tetrachloride (5 ml) was added over 5 min to a water-cooled, stirred solution of (+)-thujone (1.5 g) in carbon tetrachloride (10 ml), and the solution was stirred for 4 h at room temperature. The product was poured into ice–water containing sodium hydrogen carbonate and extracted with ether. Work up gave the *chlorothujone* (**9**) (1.5 g), b.p. 40—41 °C at 0.2—0.3 mmHg, $[\alpha]_D^{22}$ −190.6° (*c* 1.8); $\nu_{max.}$(L) 3 490sh (C=O), 3 050 (cyclopropane), 1 765 (C=O), 1 078 (C–O), and 770 cm^{-1} (Cl); δ_H 0.08 (1 H, dd, *J* 6.5, 4 Hz, 6α-H), 0.85 (1 H, ddd, *J* 8.5, 6.5, 3 Hz, 6β-H), 0.97 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 1.06 (3 H, d, *J* 6.5 Hz, 9- or 8-Me), 1.44 (1 H, hept., *J* 6.5 Hz, 7-H), 1.59 (3 H, s, 10-Me), 1.79 (1 H, dd, *J* 8.5, 4 Hz, 5-H), 2.16 (1 H, d, *J* 17.5 Hz, 2α-H), and 2.98 (1 H, dd, *J* 17.5, 3 Hz, 2β-H). An n.O.e. difference spectrum showed on saturation of the 10-Me group, a 4% enhancement of the 6α-H signal; *m/z* (f.d.) 189 (*M* + 1, 100%) and 188 (*M*$^+$, 88) (Found: *M*, 188.0782. $C_{10}H_{15}{}^{37}ClO$ requires *M*, 188.078 18).

Bromination of (−)-4-*Chlorothujone* (**9**): (−)-(1S,2S,4R,5S)-2-*Bromo*-4-*chlorothujan*-3-*one* (**12**) and (−)-(1S,2R,4R,5S)-2-*Bromo*-4-*chlorothujan*-3-*one* (**13**).—Bromine (6.15 g, 0.95 mol equiv.) in carbon tetrachloride (15 ml) was added during 40 min to a stirred solution of (−)-4-chlorothujone (7.6 g) in carbon tetrachloride (30 ml). After 4 h the mixture was poured into ice–water and the organic layer was separated, washed with aqueous sodium hydrogen carbonate and water, and dried. Evaporation of this at 30 °C under reduced pressure gave a semisolid product (10.4 g) which was kept at −10 °C for 24 h when (−)-(1S,2S,4R,5S)-2-*bromo*-4-*chlorothujan*-3-*one* (**12**) (3.9 g) separated (needles; from MeOH), m.p. 86—87 °C, $[\alpha]_D^{22}$ −19.3° (*c* 1.5); $\nu_{max.}$(N) 3 480 (C=O), 1 765 (C=O), 1 165 (C–O), and 790 cm^{-1} (CCl); δ_H −0.08 (1 H, dd, *J* 8, 4 Hz, 6α-H), 0.76 (3 H, d, *J* 7 Hz, 8- or 9-Me), 1.04 (3 H, d, *J* 7 Hz, 9- or 8-Me), 1.10 (1 H, overlapping dd, $J_{gem} = J_{cis}$ 8 Hz, 6β-H), 1.64 (3 H, s, 10-Me), 2.16 (1 H, dd, *J* 8, 4 Hz, 5-H), 2.60 (1 H, hept., *J* 7 Hz, 7-H), and 4.21 (1 H, s, 2α-H); *m/z* 159 (*M*$^+$ − Br − CO, 25%), 158 (*M*$^+$ − Br − CO, 100), 157 (*M*$^+$ − Br − CO, 17), and 129 (88) (Found: C, 45.3; H, 5.2. $C_{10}H_{14}BrClO$ requires C, 45.2; H, 5.3%). Chromatography of the mother liquors on silica using 2—4% ethyl acetate in hexane gave a further quantity (0.35 g) of (**12**) in the later fractions from the column. Early fractions gave (−)-(1S,2R,4R,5S)-2-*bromo*-4-*chlorothujan*-3-*one* (**13**) (2.8 g), which after a second run through a column was obtained as a liquid, $[\alpha]_D^{22}$ −262° (*c* 0.74); $\nu_{max.}$(L) 3 520, 1 774, 775, and 655 cm^{-1}; δ_H 0.38 (1 H, dd, *J* 7, 4 Hz, 6α-H), 1.06 (3 H, d, *J* 7 Hz, 8- or 9-Me), 1.01 (1 H, m, *J* 8, 7, 1.5 Hz, 6β-H), 1.18 (3 H, d, *J* 7 Hz, 9- or 8-Me), 1.66 (3 H, s, 10-Me), 1.75 (1 H, hept., *J* 7 Hz, 7-H), 2.15 (1 H, dd, *J* 8, 4 Hz, 5-H), and 5.35 (1 H, d, *J* 1.5 Hz, 2-H). Irradiation of the multiplet at δ 1.01 (6β-H) collapsed the d at δ 5.35 (2-H) to a s (Found: C, 45.4; H, 5.0. $C_{10}H_{14}BrClO$ requires C, 45.2; H, 5.3%).

Equilibration of (−)-(1S,2S,4R,5S)-2-*Bromo*-4-*chlorothujan*-2-*one* (**12**) *with its* 3-*Epimer* (**13**).—A mixture of the bromo chloro ketone (**12**) (0.4 g), finely powdered pyridinium bromide (1 g) and dimethyl sulphoxide (2 ml) was stirred at room temperature for 60 h. Work-up gave a pale brown oil (0.4 g), $[\alpha]_D^{20}$ −195° (*c* 3.4); $\nu_{max.}$(L) 1 770 cm^{-1}. Its ^{1}H n.m.r. spectrum showed it to be a mixture of (**13**) (*ca.* 75%) and (**12**) (25%).

Reactions of Zinc Bromide with the Bromochlorothujones (**12**) *and* (**13**).—(a) (−)-(5R,6R)-5,6-*Dibromo*-5-*isopropyl*-2-*methylcyclohex*-2-*enone* (**24**) from (**12**). A mixture of (−)-(1*S*,2*S*,4*R*,5*S*)-2-bromo-4-chlorothujone (**12**) (2.0 g), anhydrous zinc bromide (1.5 g), and dry ether (25 ml) was stirred under reflux for 40 h and then at room temperature for 100 h: Starting material had then been consumed. The product (1.5 g), $[\alpha]_D^{22}$ −0.6° (*c* 4.0); $\nu_{max.}$ (L) 1 685 cm^{-1} consisted (^{1}H n.m.r.) of a mixture of 3-bromocarvacrol (**6**)[14] and (−)-(5*R*,6*R*)-5,6-dibromo-5-isopropyl-2-methylcyclohex-2-enone (**24**) in *ca.* 16:7 proportions. Rapid chromatography on silica gave the dibromo compound (**24**) as a liquid, $[\alpha]_D^{22}$ −7.0° (*c* 1.3). Attempted further purification either by chromatography or distillation at 0.1 mmHg gave 3-bromocarvacrol.[14] The ^{1}H n.m.r. spectrum of the dibromo compound had signals at δ_H 1.06 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 1.10 (3 H, d, *J* 6.5 Hz, 9- or 8-Me), 1.88 (3 H, d, *J* 1.5 Hz, 2-Me), 2.36 (1 H, hept., *J* 6.5 Hz, 7-H), 2.84 (1 H, br d, *J* 18.5 Hz, 4β- or 4α-H), 2.95 (1 H, br d, *J* 18.5 Hz, 4α- or 4β-H), 4.87 (1 H, s, 6-H), and 6.57 (1 H, br s, 3-H). Irradiation at δ 2.36 (7-H) collapsed the two d at δ 1.06 and 1.10 (8- and 9-Me) each to a s. Irradiation of the broad s at δ 6.57 (3-H) sharpened the ABq at δ 2.95 (4α- or 4β-H) and collapsed the d at δ 1.88 (2-Me) to a s.

3-Bromocarvacrol (**6**) showed ^{1}H n.m.r. signals at δ_H 1.23 (6 H, d, *J* 6.5 Hz, 8- and 9-Me), 2.27 (3 H, s, ArMe), 3.25 (1 H, hept., *J* 6.5 Hz, 7-H), 5.57 (1 H, s, OH), 6.76 (1 H, d, *J* 8 Hz, 5-H), and 7.04 (1 H, d, *J* 8 Hz, 6-H).

(b) (+)-(5R,6S)-5,6-*Dibromo*-5-*isopropyl*-2-*methylcyclohex*-2-*enone* (**25**) *from* (**13**). A mixture of (−)-(1*S*,2*R*,4*R*,5*S*)-2-bromochlorothujone (**13**) (0.6 g), anhydrous zinc bromide (3 g), and ether (25 ml) was gently refluxed, and stirred for 5 h. Work-up gave a syrup which partially solidified at −10 °C. The solid (0.1 g) was first pressed on a porous plate and then recrystallised from aqueous methanol to give (+)-(5R,6S)-5,6-*dibromo*-5-*isopropyl*-2-*methylcyclohex*-2-*enone* (**25**) as needles, m.p. 71 °C, $[\alpha]_D^{26}$ +85.2° (*c* 0.4); $\lambda_{max.}$ 245 nm (ε 6 320); $\nu_{max.}$(N) 1 690 and 1 618 cm^{-1}; δ_H 1.01 (3 H, d, *J* 6 Hz, 8- or 9-Me), 1.08 (3 H, d, *J* 6 Hz, 9- or 8-Me), 1.90 (3 H, m, $J_{10.4\alpha}$ 2.5 Hz, $J_{10.4\beta}$ 1.5 Hz, 10-Me), 2.42 (1 H, hept., *J* 6 Hz, 7-H), 2.77 (1 H, d quintet, J_{gem} 18 Hz, $J_{3.4\alpha}$ 2.5 Hz, $J_{10.4\alpha}$ 2.5 Hz, 4α-H), 2.87 (1 H, ddq, J_{gem} 18 Hz, $J_{3.4\beta}$ 5 Hz, $J_{10.4\beta}$ 1.5 Hz, 4β-H), 4.47 (1 H, s, 6-H), and 6.55 (1 H, m, $J_{3.4\beta}$ 5 Hz, $J_{3.4\alpha}$ 2.5 Hz, 3-H). Irradiation of the 10-methyl signal at δ 1.90 collapsed the signals for the 4α- and 4β-H, in each case to a dd and simplied the 3-H m to a dd; *m/z* 312 (M^+, 2%), 310 (M^+, 7) 308 (M^+, minor), 268 (8), 266 (42), 264 (31), 231 (M^+ − Br, 30), 229 (M^+ − Br, 30), 228 (M^+ − Br, 14), 121 (96), and 82 (100) (Found: *M*, 309.9445. $C_{10}H_{14}{}^{79}Br^{81}BrO$ requires *M*, 309.9391).

An impurity present to varying degrees in different preparations of the enone (**25**) had identical ^{1}H n.m.r. signals except for the 6-H, 7-H, and isopropyl methyls, which were of the same multiplicity but of slightly different chemical shifts. The most probable structure for this impurity is that of the 5-epimer with an α-Br constituent.

Reaction of 4-chlorothujone (**9**) with zinc bromide in ether, rapidly gave carvacrol quantitatively.

Reaction of Bromine with (−)-(1S,2R,4R,5S)-2-*Bromo*-4-*chlorothujan*-3-*one* (**13**) *in Light:* (1S,2R,4R,5S)2,7-*Dibromo*-4-*chlorothujan*-3-*one* (**20**).—A solution of the bromo chloro compound (**13**) in $CDCl_3$ (11.5 mg in 1.2 ml) (0.6 ml) was treated with 0.056 ml of a solution of bromine (0.4 ml) in carbon tetrachloride (10 ml) and the solution was kept in the dark for 24 h. Intermittent examination by ^{1}H n.m.r. spectroscopy showed that no reaction had taken place. The solution was then exposed to ordinary laboratory light (Thorn T40W/35 white fluorescent tube) for 7.25 h when ^{1}H n.m.r. spectroscopy showed the smooth formation of (**20**) as sole product; δ_H 0.65 (1 H, dd, *J* 7.5 Hz, 6α-H), 1.59 (1 H, ddd, *J* 8, 7, 2 Hz, 6β-H), 1.69 (3 H, s, 10-Me), 1.82 (3 H, s, 8- or 9-Me), 2.06 (3 H, s, 9- or 8-Me), 2.64 (1 H, dd, *J* 8, 5 Hz, 5-H), and 5.67 (1 H, d, *J* 2 Hz, 2-H). No attempt was made to isolate the dibromo chloro product.

(−)(1S,4R,5S)-4-*Methoxythujan*-3-*one* (**14**).—A solution of (−)-4-chlorothujone (**9**) (1.0 g) in methanolic sodium methoxide (2.5%; 10 ml) was set aside overnight. Work-up gave the *methyl ether* (**14**) (0.9 g), b.p. 35 °C at 0.3 mmHg; $[\alpha]_D^{22}$ −17.1° (*c* 0.6); $\nu_{max.}$(L) 3 035 (cyclopropane), 2 832 (MeO), 1 745 (C=O), and 1 112 cm^{-1} (MeO); δ_H −0.3 (1 H, dd, *J* 6.5, 4 Hz, 6α-H), 0.75 (1 H, ddd, *J* 9, 6.5, 3 Hz, 6β-H), 0.92 (3 H, d, *J* 7 Hz, 8- or 9-Me), 1.02 (3 H, d, *J* 7 Hz, 9- or 8-Me), 1.22 (3 H, s, 10-Me), 1.47 (1 H, overlapping dd, *J* 9, 4 Hz, 5-H), 1.50 (1 H, overlapping hept., *J* 7 Hz, 7-H), 2.13 (1 H, d, *J* 18 Hz, 2α-H), 2.70 (1 H, dd, *J* 18, 3 Hz, 2β-H), and 3.20 (3 H, s, MeO). N.O.e. difference spectra gave the following: saturation of the OMe group gave 1.25 and 2% enhancements for the 10-Me and 5-H signals respectively. Saturation of the 10-Me group gave a 5% enhancement for both 5α- and 6α-H signals; *m/z* 182 (M^+, 17%), 122 (M^+ − MeOH − CO, 80), and 107 (M^+ − MeOH − C_3H_7, 100) (Found: *M*, 182.1300. $C_{11}H_{18}O_2$ requires *M*, 182.1307). The methyl ether (**14**) was also formed when 4-chlorothujone was treated with 5% methanolic potash.

(−)-(1S,4R,5S)-4-*Diethylaminothujan*-3-*one* (**15**).—Diethylamine (0.7 g) was added to a solution of (−)-4-chlorothujone (**9**) (0.2 g) in chloroform (2 ml). After 12 h, work-up gave the *amine* (**15**) (0.2 g), b.p. 62 °C at 0.5 mmHg; $[\alpha]_D^{22}$ −8.2° (*c* 4.0); $\nu_{max.}$(L) 3 460 (C=O), 3 050 (cyclopropane), and 1 745 cm^{-1}; δ_H −0.12 (1 H, dd, *J* 6, 4 Hz, 6α-H), 0.66 (1 H, ddd, *J* 8.5, 6, 3 Hz, 6β-H), 0.84 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 0.98 [6 H, t, *J* 7 Hz, $N(CH_2Me)_2$], 0.99 (3 H, d, *J* 6.5 Hz, 9- or 8-Me), 1.05 (3 H, s, 10-Me), 1.49 (1 H, dd, *J* 8.5, 4 Hz, 5-H), 1.61 (1 H, hept., *J* 6.5 Hz, 7-H), 2.11 (1 H, d, *J* 17 Hz, 2α-H), 2.65 [5 H, m, 2β-H and $N(CH_2Me)_2$]. N.O.e. difference spectra showed on saturation of the 6α-H signal enhancements of 1, 2, and 20% for the 10-Me group, 2α-H and 6β-H signals respectively. Saturation of the 10-Me group signal gave a 7% enhancement of the 6α-H signal; *m/z* 223 (M^+, 8%), 195 (M^+ − CO, 30), 180 (M^+ − Me − CO, 90), 166 (37), 152 (57), 126 (34), 113 (30), 112 (56), 86 (66), 70 (40), and 43 (100) (Found: *M*, 223.1939. $C_{14}H_{25}NO$ requires *M*, 223.1936).

Bromination of (−)-*Carvotanacetone* (**19**).—(a) *With* 2 *mol equiv. of Bromine.* (−)-(2R,3S,5S,6S)-2,3,6-*Tribromo*-5-*isopropyl*-2-*methylcyclohexanone* (**27**) *and* (+)-(2R,3R,5S,6S)-2,3,6-*tribromo*-5-*isopropyl*-2-*methylcyclohexanone* (**28**). A solution of bromine in acetic acid (10%; 43 ml) was added over 1 h to a stirred, ice-cold solution of (−)-carvotanacetone {2 g; $[\alpha]_D^{25}$ −52.5° (*c* 1.5) in acetic acid (13 ml)}. Stirring was continued for 12 h. Work-up gave a semisolid (4.8 g, 93%) which was crystallised from light petroleum (b.p. 40—60 °C), to give (−)-(2R,3S,5S,6S)-2,3,6-*tribromo*-5-*isopropyl*-2-*methylcyclohexanone* (**27**) as needles (1 g), m.p. 132 °C, $[\alpha]_D^{22}$ −45.1° (*c* 1.0); $\nu_{max.}$ (N) 1 740, 1 180, 1 160, 1 070, 1 050, and 725 cm^{-1}; δ_H 0.91 (3 H, d, *J* 6.5 Hz, 8- or 9-Me), 1.02 (3 H, d, *J* 6.5 Hz, 9- or 8-Me), 1.79 (1 H, m, 5-H), 2.02 (3 H, s, 10-Me), 2.36 (3 H, m, 4-CH_2 and 7-H), 3.82 (1 H, dd, *J* 12, 5 Hz, 3-H), and 5.52 (1 H, d, *J* 13 Hz, 6-H). Irradiation of the m at δ 2.36 (4-CH_2 and 7-H) collapsed the dd at δ 3.82 (3-H) to a s, the two d at δ 0.91 and 1.02 (8- and 9-Me) each to a s and the m at δ 1.79 (5-H) to a d. A n.O.e. difference spectrum showed that saturation of the 10-Me group gave a 9.6% enhancement of the 3-H signal, but had no effect on the 6-H signal; *m/z* 394, 392, 390, 388 (M^+, combinations of ^{79}Br and ^{81}Br), 313 (M^+ − ^{81}Br, 41%), 311 (86), 309 (42), and 53 (100) (Found: C, 30.7; H, 4.0. $C_{10}H_{15}Br_3O$ requires C, 30.7; 3.9%).

The mother liquors from which (**27**) separated and mother liquors from its crystallisation were bulked and chromatographed on silica using 5% ethyl acetate in hexane as eluant. Early fractions afforded (+)-(2R,3R,5S,6S)-2,3,6-*tribromo*-5-*isopropyl*-2-*methylcyclohexanone* (**28**) (1.6 g), m.p. 48—50 °C (MeOH); $[\alpha]_D^{20}$ +64.5° (*c* 1.7); $\nu_{max.}$(N) 1 740, 1 062, and 735 cm^{-1}; δ_H 0.93 (3 H, d, *J* 7 Hz, 8- or 9-Me), 0.99 (3 H, d, *J* 7 Hz, 9- or 8-Me), 2.06 (3 H, s, 10-Me), 2.20 (1 H, dt, *J* 15, 3 Hz, 4β-H), 2.39 (1 H, m, 7-H), 2.58 (1 H, tt, *J* 13, 3 Hz, 5-H), 2.78 (1 H, ddd, *J* 15, 13, 3 Hz, 4α-H), 4.78 (1 H, t, *J* 3 Hz, 3-H), and 5.47 (1 H, d, *J* 13 Hz, 6-H). Irradiation of the d at δ 5.47 (6-H) collapsed the tt at δ 2.58 (5-H) to a dt. Irradiation of the t at δ 4.78 (3-H) collapsed the signals at δ 2.20 (4β-H) and δ 2.78 (4α-H) each to a dd. On saturation of the 10-Me signal, a n.O.e. difference spectrum revealed a 6.5% enhancement of the 3α-H signal (Found: C, 30.5; H, 4.0. $C_{10}H_{15}Br_3O$ requires C, 30.7; H, 3.9%).

Later fractions from the column gave more (**27**) (0.3 g), m.p. 128—130 °C. Final fractions gave 5-bromocarvacrol (**7**) (0.1 g); δ_H 1.09 (6 H, d, *J* 6.5 Hz, 8- and 9-Me), 2.18 (3 H, s, *Me*Ar), 3.25 (1 H, hept., *J* 6.5 Hz, 7-H), 4.78 (1 H, s, OH), 6.69 (1 H, s, 3-H), and 7.26 (1 H, s, 6-H) identical with the spectrum of authentic 5-bromocarvacrol.[15]

(b) *With 1 mol equiv. of bromine* (cf. *ref.* 10). (+)-(2R,3R,5S)-2,3-*Dibromo-5-isopropyl-2-methylcyclohexanone* (**29**). Bromine in acetic acid (10%; 10.3 ml) was added rapidly to a stirred solution of (−)-carvotanacetone (**19**) (1 g) in acetic acid (6 ml) Uptake of bromine was rapid. The solution was added to water (100 ml) and extracted thrice with ether, from which a colourless oil (1.9 g) was obtained: t.l.c. showed that it was mainly one component. It was chromatographed on silica using 3% ethyl acetate in hexane to give (+)-(2R,3R,5S)-2,3-*dibromo-5-isopropyl-2-methylcyclohexanone* (**29**), $[\alpha]_D^{20}$ +138.3° (*c* 1.15), $\nu_{max.}$(L) 1 724 cm^{-1}; δ_H 0.96 (6 H, 2d, each *J* 6.5 Hz, 8- and 9-Me), 1.66 (1 H, octet, *J* 6.5 Hz, 7-H), 2.00 (3 H, s, 10-Me), 2.17 (1 H, d, br, *J* 15 Hz, 4β-H), 2.32 (1 H, m, 5-H), 2.45 (1 H, ddd, *J* 15, 4, 2 Hz, 6β-H), 2.67 (1 H, ddd, *J* 15, 12, 3 Hz, 4α-H), 3.05 (1 H, dd, *J* 15, 12 Hz, 6α-H), and 4.80 (1 H, t, *J* 3 Hz, 3α-H). Irradiation of the m at δ 3.05 (6α-H) collapsed the m at δ 2.45 (6β-H) to a dd. Irradiation of the t at δ 4.80 (3α-H) collapsed the m at δ 2.67 (4α-H) to a dd. On saturation of the 10-Me group, a n.O.e. difference spectrum showed a 6% enhancement of the 3α-H signal at δ 4.80, but no other significant enhancements; *m/z* 314 (0.37%), 312 (0.73), 310 (0.5), 223 (14), 231 (15), 152 (35), 109 (28), 72 (100), and 71 (48) (Found: *M*, 311.9544; C, 38.4; H, 5.0. $C_{10}H_{16}{}^{79}Br^{81}BrO$ requires *M*, 3111.9544; C, 38.5; H, 5.2%).

(c) *With an excess of bromine in tetradeuterioacetic acid and deuteriochloroform.* (−)-Carvotanacetone (5.4 mg) in tetradeuterioacetic acid (0.3 ml) and deuteriochloroform (0.2 ml) was treated with 5 μl of a solution of bromine (0.1 ml) in tetradeuterioacetic acid (0.4 ml). 360 ^{1}H N.m.r. spectra were measured at suitable intervals during the following days. Within 30 min, the carvotanacetone had been completely converted into (2*R*,3*R*,5*S*)-2,3-dibromo-5-isopropyl-2-methylcyclohexanone (**29**) and further bromine solution (30 μl) was added. After 24 h, almost all the dibromide (**29**) had disappeared and the main product (amongst others formed) was (2*R*,3*R*,5*S*,6*S*)-2,3,6-tribromo-5-isopropyl-2-methylcyclohexanone (**28**). After a further 6 days the tribromide (**28**) had isomerised to the extent of *ca.* 50% to the 3-epimer (2*R*,3*S*,5*S*,6*S*)-2,3,6-tribromo-5-isopropyl-2-methylcyclohexanone (**27**), identified by enrichment with the pure (−)-isomer. Other products, not identified, were also present.

Reaction of (±)-*Carvenone* (**31**) *with an Excess of Bromine in Deuteriochloroform–Carbon Tetrachloride.*—A solution of (±)-carvenone (15.2 mg) in deuteriochloroform (1.2 ml) (0.4 ml) was treated with a solution of bromine (1 ml) in carbon tetrachloride (25 ml) (0.16 ml) and ^{1}H n.m.r. spectra were run at suitable intervals. After 4 min, the solution showed that the olefinic signal at δ 5.85 in the starting material had completely disappeared and was replaced by three barely separated signals centred on δ 4.63 [6 H of (**33**) and (**34**)]. The mixture also showed distinct signals at δ 1.47 [d, *J* 6.5 Hz, 2-Me of (**33**)], and 3.26 [*J* 6.5 Hz, 2 overlapping quintets, 7-H of (**34**)].

Within 3 h, the mixture had been transformed to a virtually pure sample of the single diastereoisomeric tribromide (**35**); δ_H 1.06 (3 H, d, *J* 7 Hz, 8- or 9-Me), 1.15 (3 H, d, *J* 7 Hz, 9- or 8-Me), 1.95 (3 H, s, 2-Me), 2.16 (1 H, hept., *J* 7 Hz, 7-H), 2.20 (1 H, m, 4α-H), 2.38 (1 H, ddd, *J* 15, 11.5, 4 Hz, 4β-H), 2.57 (1 H, m, ddd, *J* 15, 11.5, 4 Hz, 3β-H), 2.68 (1 H, ddd, *J* 15, 11.5, 4 Hz, 3α-H), 4.72 (1 H, d, *J* 2.5 Hz, 6α-H). Irradiation of the d at δ 4.72 (6α-H) simplified the m at δ 2.20 (4α-H) to a ddd, removing the W coupling to the 6α-H. N.O.e. difference spectra showed that saturation of the 2-Me group gave a 4% enhancement of the 3α-H whilst saturation of the isopropyl methyl signals gave 19 and 10.5% enhancements of the 7- and 6-H signals respectively. Subsequently, transformations of the tribromide (**35**) took place which were not investigated in detail.

References

1 Part 26, W. Cocker, R. L. Gordon, and P. V. R. Shannon, *J. Chem. Res.*, 1985, (*S*), 172; (*M*), 2101.
2 O. Wallach, *Liebigs. Ann. Chem.*, 1893, **275**, 179; 1895, **286**, 109.
3 S. P. Acharya, H. C. Brown, A. Suzuki, S. Nozawa, and M. Itoh, *J. Org. Chem.*, 1969, **34**, 3015.
4 T. Norin, *Acta Chem. Scand.*, 1962, **16**, 640.
5 R. H. Eastman, P. M. Iloff, and H. Isaacs, *J. Am. Chem. Soc.*, 1958, **80**, 1704.
6 P. de Mayo, in 'Molecular Rearrangements,' Wiley, London. 1964, part 2, p. 807.
7 H. P. Rothbaum, I. Ting, and P. W. Robertson, *J. Chem. Soc.*, 1948, 980 and earlier refs. given there.
8 M. A. Cooper, C. M. Holden, P. Loftus, and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1973, 665.
9 R. P. Houghton, 'Metal Complexes in Organic Chemistry,' Cambridge University Press, Cambridge, 1979, pp. 148—149.
10 O. Wallach, *Liebigs Ann. Chem.*, 1918, **414**, 271.
11 H. E. Zimmerman, D. Döpp, and P. S. Huyffer, *J. Am. Chem. Soc.*, 1966, **88**, 5352; T. M. Brennan and R. K. Hill, *ibid.*, 1968, **90**, 5614.
12 W. Cocker, T. B. H. McMurry, and B. Wheeler, *J. Sci. Food Agric.*, 1958, **9**, 828.
13 V. Hach, R. W. Lockhart, E. C. McDonald, and D. M. Cartlidge, *Can. J. Chem.*, 1971, **49**, 1762.
14 J. Novák and C. A. Salemink, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2873.
15 O. Wallach and F. Neumann, *Chem. Ber.*, 1895, **28**, 1660.

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