ON THE METHYLATION OF (+)-CARVONE—I

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Abstract—The methylation of (+)-carvone with methyl iodide in the presence of potassium *t*-butoxide gave 6,6′,10,10′-tetramethyl-3,12-diisopropenyl-tricyclo-[6.2.2.0^{2,7}]-dodecana-5,9-dione (II; R = Me and the 6,10,10′-trimethyl analogue (II; R = H). The evidence for these structures is presented.

THE dimerization of cyclohexones in the presence of bases can give rise to a wide variety of products,[1] and considerable interest attaches to determining their structures. This paper reports the structures of two compounds produced in the methylation of (+)-carvone I with methyl iodide and potassium t-butoxide in t-butanol. The problem is complicated here by the fact that the cyclohexenone, (+)-carvone, has an asymmetric centre, a feature absent in the cases previously discussed.[1]

Steroidal $\alpha\beta$-unsaturated ketones are normally methylated at the α-position with methyl iodide and potassium t-butoxide in t-butanol at 40.[2] (+)-Carvone I under these conditions gave a solid, m.p. 139–140°, which was resolved by chromatography on alumina into two components, A (II; R = Me) the minor component, m.p. 150–151°, and B (II; R = H), m.p. 129–130°.* The mol wts of these compounds, 328 and 314 respectively, suggested that they were dimers of (+)-carvone with two and one additional Me groups respectively. This was supported by the microanalysis figures for both compounds. A therefore has the molecular formula $C_{22}H_{32}O_2$ and B the formula $C_{21}H_{30}O_2$. Both compounds were recovered from a refluxing solution of potassium t-butoxide in t-butanol, and further, compound B could be converted into compound A by adding methyl iodide to its solution in hot t-butanol containing potassium t-butoxide. Thus the problem was simplified to that of determining the structure of the common carbocyclic skeleton of A and B, and then to specifying the positions of methylation.

I   II; R = Me; A
   R = H; B
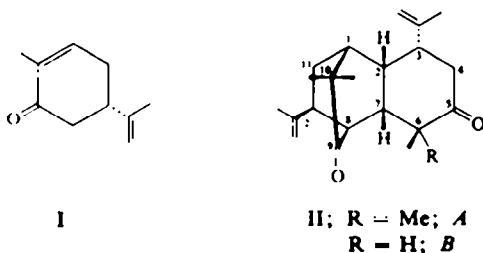
* The chemistry of the volatile components of the reaction product, monocyclic methylation products, will be reported in a future paper.

[1] *Inter alia*, G. Büchi, J. H. Hansen, D. Knutson and E. Koller, *J. Am. Chem. Soc.* **80**, 5517 (1958); N. J. Leonard and W. J. Musliner, *J. Org. Chem.* **31**, 639 (1966).
[2] F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.* **79**, 2906 (1957).

Both *A* and *B* were completely inert towards the usual carbonyl reagents, suggesting that both CO groups are considerably hindered. Hydrogenation of either compound on Pt in ethanol led to the rapid uptake of 1 mole of hydrogen, followed by the rather slower uptake of a second mole. This suggests that one of the isopropenyl groups is in rather a hindered position. The tetrahydro derivatives were saturated, since they gave no colour with tetranitromethane, their UV spectra showed no appreciable end-absorption, and further the oily acetates of the alcohols III (R = H and R = Me) obtained by the reduction of the tetrahydro derivatives with LAH, were inert towards *p*-nitroperbenzoic acid. Therefore *A* and *B* are tricyclic.

III; R = H   IV; R = H
     R = Me   R = Me
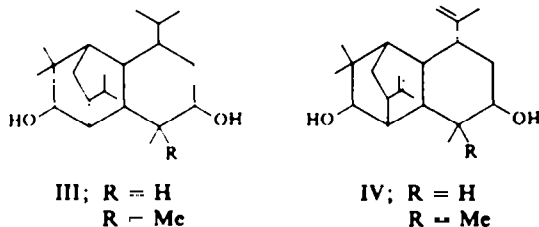
The spectra of the compounds *A* and *B* yielded valuable information as to their structures. In the IR spectra of both compounds two CO frequencies were observed at 1710 and 1720 cm^{-1}. The first of these falls within the range for substituted cyclohexanones, while the other indicated a CO on a bridging ethano group.[3] The IR spectra also showed two different methylene absorptions (at 900, 895 cm^{-1} for *A* and at 893, 890 cm^{-1} for *B*) indicating two isopropenyl groups in different environments. This was supported by the NMR spectra in which two different resonances due to the Me groups of the isopropenyl side-chains were observed (8·28 and 8·39 τ). The chemical shift between these, 7 c/s, is in fact rather greater than that usually observed, 3–4 c/s, between the Me groups of axial and equatorial isopropenyl side-chains,[4] and it seemed reasonable to suppose that one of the Me groups in question was falling partly within the shielding cone of one of the CO groups.[5]

The NMR spectrum of *A* showed two sharp though slightly broad singlets at 8·85 and 9·00 τ each corresponding to six protons. These signals could arise from either four coincident doublets due to four >CH—Me systems, from two coincident doublets due to two >CH—Me systems and two singlets due to two quaternary Me groups, or from four singlets (grouped in two pairs) due to four quaternary Me groups. A decision between these possibilities was made on the basis of the following arguments. In the original carvone molecule, the Me group is in the α-position to the CO. Since there are known to be four Me groups in *A* (two from the original two molecules of carvone and two from further methylation), and since methylation under these reaction conditions can only occur at α-positions to the CO groups, four >CH—Me systems would imply four hydrogen atoms α to the CO groups. If this were so, then deuteration of *A* should lead to the uptake of four deuterium atoms. In fact the deuteration of *A* in EtOD/D$_2$O containing NaOD led to the uptake of two deuterium atoms only. Thus there cannot be four >CH—Me systems in *A*.

[3] R. Zbinden and H. K. Hall, *J. Am. Chem. Soc.* **82,** 1215 (1960).
[4] D. L. Robinson and D. W. Theobald, unpublished work.
[5] M. L. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 122. Pergamon, London (1959).

The NMR spectrum of A and its dideuterated derivative were identical in the region of resonance under consideration. Since the Me resonance of $>$CH—Me, would be a doublet (J ≈ 6 c/s) and of $>$CD—Me a singlet (perhaps slightly broadened) this observation excludes the presence of two $>$CH—Me systems in A. Thus it must be that in A there are four quaternary Me groups, in this case most likely two

$$\begin{array}{c} \text{Me} \\ \diagdown \diagup \\ \text{C} \\ \diagup \diagdown \\ \text{Me} \end{array}$$
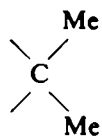
systems. These arguments were supported by the fact that the chemical

shift between these two resonances (at 8·85 and 9·00 τ) depended upon the oscillator frequency (60 and 100 Mc/s), showing that their separation was in fact a chemical shift and was not due to spin-spin coupling.

If the possibility of the formation of small or medium rings is discounted, the structures shown in Fig. 1 are mechanistically acceptable as candidates for the parent structure of A and B. They arise from two successive Michael reactions involving the addition of a carbanion to the β-position of an $\alpha\beta$-unsaturated carbonyl system. The dimerization is then followed by methylation, monomethylation to give B, and dimethylation to give A.

It is not difficult to see that pathway (b) leading to structure VI is correct, for the following reasons. Structure V when dimethylated would yield a system in which no deuterium-hydrogen exchange would be possible. Compound A however takes up two deuterium atoms on exchange. Pathway (a) and structure V are therefore unacceptable.

Pathway (c) leading to structure VII apart from the fact that it involves an unlikely Michael reaction with a tertiary carbanion, can be excluded by considering the possible products of methylation of structure VII. Dimethylation would result

in the systems $\begin{array}{c} \text{Me} \\ \diagdown \diagup \\ \text{C} \\ \diagup \diagdown \\ \text{Me} \end{array}$, $>$CH—Me and $\begin{array}{c} \diagdown \\ —\text{C}—\text{Me.} \\ \diagup \end{array}$ But this cannot be accommo-

dated by the NMR spectrum of A which was interpreted in terms of two $\begin{array}{c} \text{Me} \\ \diagdown \diagup \\ \text{C} \\ \diagup \diagdown \\ \text{Me} \end{array}$

systems (or at least four quaternary Me groups). Neither would structure VII be compatible with the exchange by A of two hydrogen atoms for deuterium.

Further evidence against VII comes from the product of dimerization of (+)-carvone in the presence of t-butoxide ion. The NMR spectrum of the dimer (from which A and B could be obtained by methylation), showed two doublets (3 protons each) centred at 8·82 (J = 6 c/s) and 8·95 τ (J = 6 c/s) indicating the presence of two $>$CH—Me systems. This is clearly incompatible with structure VII as the parent of compounds A and B. The mechanistically unlikely possibility of a simple direct dimerization across the conjugated double bonds (Fig. 2) with the formation of a cyclobutane ring[6] VIII is also excluded on this basis. Moreover such a structure

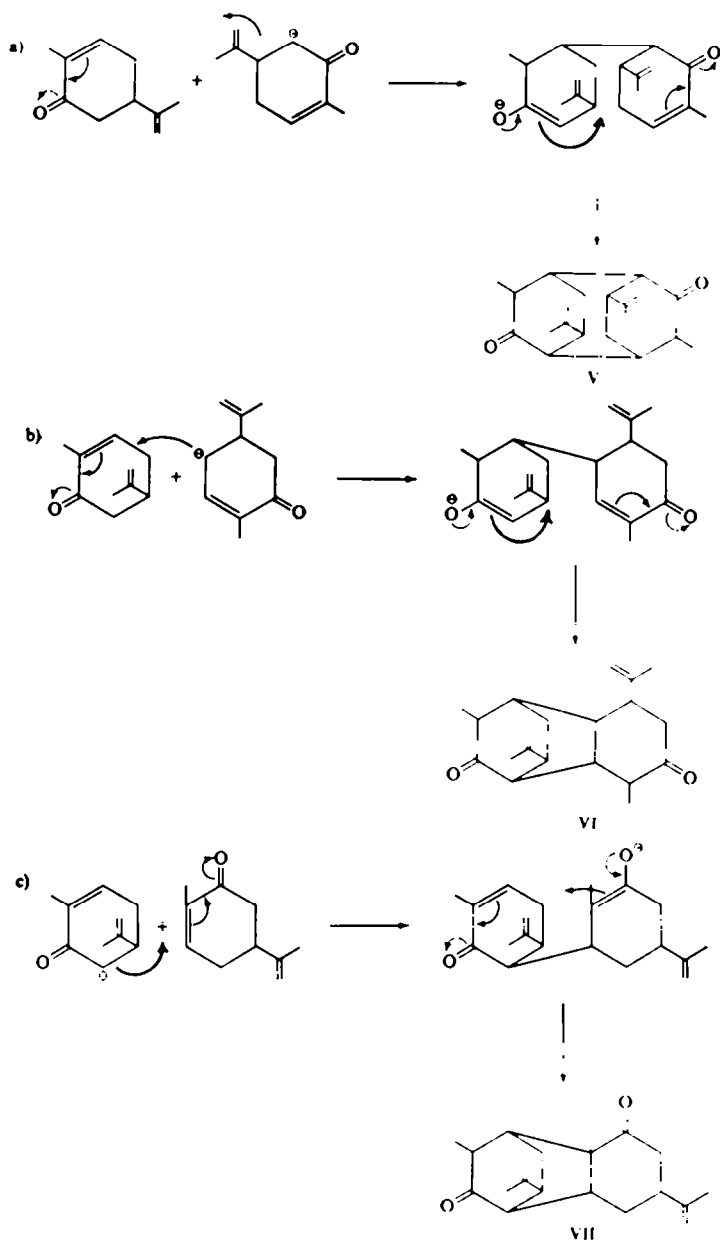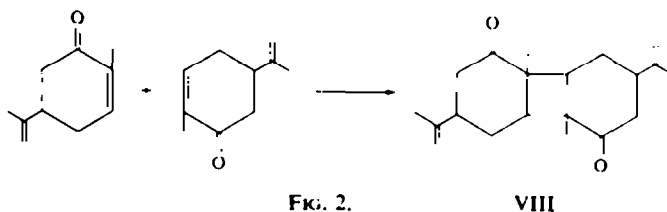[6] P. E. Eaton, *J. Am. Chem. Soc.* **84**, 2344, 2454 (1962).

Fig. 1

cannot accommodate the two IR CO frequencies of 1710 and 1715–1720 cm^{-1} observed in these compounds.

FIG. 2.   VIII

This leaves pathway (b) as the most likely, and it remains to specify the stereochemistry of VI. There are four possibilities for compound *A*, IX, X, XI, and XII, taking into account the stereochemistry of (+)-carvone I.

IX   X

XI   XII
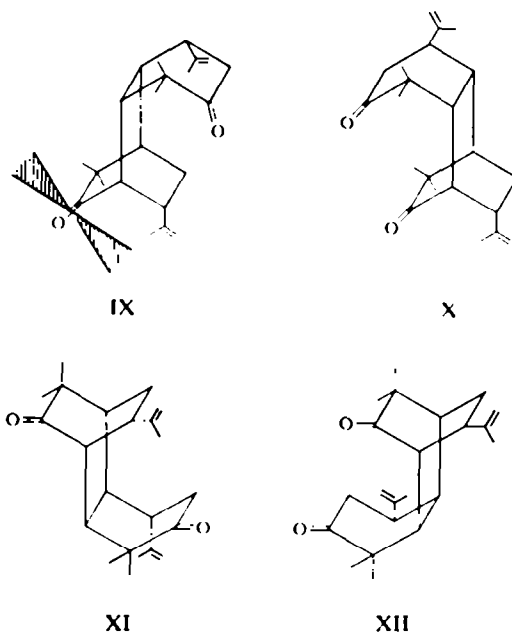
It was noted in discussing the NMR spectra of *A* and *B* that there was a considerable difference (7 c/s) in the resonance frequency of the Me groups in the isopropenyl side-chains. This can only be accounted for on the basis of the structures IX or X since in these one of the isopropenyl groups falls partly within the shielding cone of a CO group.[6] Further the NMR spectrum of the dihydro derivative of *A* showed that it was this isopropenyl group which was the more difficult to hydrogenate.

The structures IX and X imply that the initial Michael addition of one carvone molecule to the other takes place so that the incoming carbanion approaches the face of the molecule which does not carry the isopropenyl group. This is in accord with the results of other investigators on the nucleophilic attack at the β-position of the αβ-unsaturated CO system of cyclohexenones. Thus Djerassi *et al.* found that the addition of cyanide ion to carvone occurs predominantly from the side opposite

the isopropenyl group.[7] And more recently, Allinger and Riew investigated the 1,4-addition of MeMgBr to 5-methyl-cyclohex-2-enone.[8] They found that the addition gave exclusively *trans*-3,5-dimethylcyclohexanone, indicating that the reagent approaches preferentially the face of the molecule which does not carry the substituent. They discussed this in terms of the conformational energies of the various boat-like and chair-like transition states open to the system.

Given that the initial Michael addition follows this pattern, a second addition leaves two possibilities open, IX or X depending upon whether the second ring is *exo* or *endo* to the CO bridge. On stereoelectronic grounds the alternative IX is clearly favoured, and Dreiding models show that steric interactions which would be important during the formation of the second bond between the rings[8] are in fact less in IX than in X. Models also show that the system IX has a certain limited flexibility, and that the optimum conformation of the molecule is such that the second ring is a slightly deformed boat XIII.

All the available evidence therefore points to the structure IX ≡ II (R ≡ Me) as the most likely for *A*. Such a structure accounts for the unreactivity of the CO groups, the non-equivalence of the isopropenyl groups, the NMR and IR spectra, and the exchange of two hydrogen atoms for deuterium. The question of the position of the single Me group in *B* remains to be discussed. Information on this point came from the dehydration of the diol III (R = H) from the reduction of the tetrahydro derivative of *B* with LAH. Dehydration with phosphorus oxychloride in pyridine at 5°, a reaction not usually considered to involve carbonium ions as intermediates, gave an oily product containing an OH group (IR 3430 cm^{-1}) and a $\overset{\displaystyle |}{C}=\overset{\displaystyle |}{\underset{\displaystyle |}{C}}-Me$ system (NMR 8·33 τ). This product, presumably XIV can easily be accounted for on the basis of the structure II (R = H) for *B*, but less easily on the alternative structure
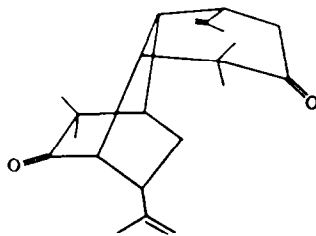

XIII

for *B* with the single Me group at position 10. There is no question but that the OH group at position 5 would be removed easily under these dehydration conditions whatever the degree of methylation at position 6. However that at position 9 might still be resistant to dehydration even if the single Me group were at position 10; for it is not inconceivable that there might be some difficulty in the abstraction of the proton from position 10 by the base. If this were the case however, no resonance due to a $\overset{\displaystyle |}{\underset{\displaystyle |}{C}}=\overset{\displaystyle |}{C}-Me$ would be observed in the NMR spectrum, whereas if it were not,

[7] C. Djerassi, R. A. Schneider, N. Vorbrueggen and N. L. Allinger, *J. Org. Chem.* **28**, 1632 (1963).
[8] N. L. Allinger and C. K. Riew, *Tetrahedron Letters* 1269 (1966).

then no OH absorption would be evident in the IR spectrum. The dehydration product must therefore be given the structure XIV and B the structure II (R = H).
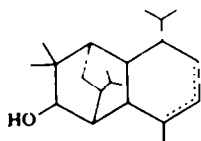
XIV

EXPERIMENTAL

M.ps are uncorrected. Specific rotations—Chf solns at 20°. UV spectra—EtOH solns, Unicam SP 700. IR spectra—Perkin-Elmer spectrophotometers PE-21 and Infracord 137 with NaCl prisms. NMR spectra—PE-R 10 instrument at 60 Mc/s. Mass spectra—AEI MS-2H instrument.

Al$_2$O$_3$ for chromatography—Peter Spence's Grade H, deactivated with 5% of 10% AcOH. Petroleum ether—b.p. 60–80°, unless otherwise stated.

The reaction of (+)-*carvone with methyl iodide and potassium t-butoxide.* (+)-Carvone (11·1 g) was added to a soln of potassium t-butoxide (from 10·0 g K) in t-butanol (180 ml) at 40° under N. To the orange-red soln so formed, MeI (28 ml) was added in small portions at 40° during 3 hr. The mixture was cooled and diluted with water, and the product recovered in ether as a viscous oil. This oil (10 g) was diluted with pet. ether (b.p. 30–40°) at 0° to give prisms (1·8 g), m.p. 139–140°. This solid was adsorbed on alumina (100 g). Elution with pet. ether–ether (10:3; 500 ml) gave 6,6,′10,10′-*tetramethyl*-3,12-*diisopropenyl*-*tricyclo*-[6.2.2.0^{3,7}]-*dodecana*-5,9-*dione* (A; II; R = Me) which crystallized from pet. ether as prisms (0·5 g), m.p. 150–151°; [α]$_D$ −33° (c, 1·2). IR (Nujol): 1720, 1710, 1645, 900, 895 cm^{-1}. UV: λ$_{max}$ 296 mμ (ε = 97). NMR (CDCl$_3$/TMS): 5·05(m), 5·15(m) (2 protons each; —C(CH$_2$)—CH$_3$), 8·28(s), 8·39(s) (3 protons each; —C(CH$_2$)·=CH$_3$),

8·85(broad s), 9·00(broad s) $\left(6 \text{ protons each; } \overset{\displaystyle\diagdown}{\underset{\displaystyle\diagup}{—C}}—CH_3 \right)$ τ. Mol. wt. (by mass spectrometry) 328.

(Found: C, 80·2; H, 9·8. C$_{22}$H$_{32}$O$_2$ requires: C, 80·5; H, 9·8%; mol. wt. 328.)

Further elution with pet. ether–ether (10:3; 200 ml) gave material (0·3 g), m.p. 137–144°, a mixture of A and B.

Still further elution with the same solvent (600 ml) gave 6,10,10′-*trimethyl*-3,12-*diisopropenyl*-*tricyclo*-[6.2.2.0]^{3,7}-*dodecana*-5,9-*dione* (B; II; R = H) which crystallized from pet. ether as prisms (0·9 g), m.p. 129–130°; [α]$_D$ −61° (c, 2·5). IR (Nujol): 1715, 1710, 1645, 893, 890 cm^{-1}. UV: λ$_{max}$ 295 mμ (ε = 89). NMR (CDCl$_3$/TMS): 5·05(m), 5·15(m) (2 protons each; —C(CH$_3$)=CH$_2$), 8·28(s), 8·38(s) (3 protons each; —C(CH$_3$)C=CH$_2$), 8·80, 8·95(d) (3 protons; —CH—CH$_3$; J = 9 c/s),

8·85(s) (3 protons), 9·00(s) (3 protons) $\left(\overset{\displaystyle\diagdown}{\underset{\displaystyle\diagup}{—C}}—CH_3 \right)$ τ. Mol. wt. (by mass spectrometry) 314. (Found:

C, 80·5; H, 9·5. C$_{21}$H$_{30}$O$_2$ requires: C, 80·3; H, 9·6%; mol. wt. 314.)

Hydrogenations on platinum in ethanol. A (II; R = Me) took up 1 mole H$_2$ to give a *dihydro derivative* which crystallized from pet. ether as prisms, m.p. 100–101°; [α]$_D$ −32° (c, 2·6). IR (Nujol): 1720, 1710, 893 cm^{-1}. NMR (CDCl$_3$/TMS): 5·15(m) (2 protons; —C(CH$_3$)=CH$_2$), 8·39(s) (3 protons; —C(CH$_3$)=CH$_2$) τ. (Found: C, 80·0; H, 10·2. C$_{22}$H$_{34}$O$_2$ requires: C, 80·0; H, 10·3%.)

A took up 2 moles H$_2$ to give the *tetrahydro derivative* which crystallized from pet. ether at 0° as prisms, m.p. 91–92°; [α]$_D$ −27° (c, 2·8). IR (Nujol): 1720, 1710 cm^{-1}. UV: λ$_{max}$ 295 mμ (ε = 95). (Found: C, 79·3; H, 10·7. C$_{22}$H$_{36}$O$_2$ requires: C, 79·5; H, 10·8%.)

B took up 2 moles H$_2$ to give the *tetrahydro derivative* which crystallized from pet. ether at 0° as prisms, m.p. 70–72°; [α]$_D$ −53° (c, 3·1). IR (Nujol): 1720, 1708 cm^{-1}. UV: λ$_{max}$ 296 mμ (ε = 105). (Found: C, 79·2; H, 10·5. C$_{21}$H$_{34}$O$_2$ requires: C, 79·3; H, 10·7%.)

The diol III (R = Me). The tetrahydro derivative of A was reduced with LAH in ether in the usual way to give *the diol* (III; R = Me) which crystallized from pet. ether as needles, m.p. 175–176°; [α]$_D$ −15° (c, 1·8). UV: ε$_{2060}$ 360. (Found: C, 78·3; H, 11·9. C$_{22}$H$_{40}$O$_2$ requires: C, 78·6; H, 11·9%.)

This diol was also obtained by the hydrogenation of the diol IV (R = Me).

The diol III (R = H). The tetrahydro derivative of *B* reduced in the usual way with LAH in ether gave *the diol* (III; R = H) which crystallized from pet. ether as needles, m.p. 147-149°; $[\alpha]_D$ −5° (*c*, 3·6). UV: ε_{3440} 410. (Found: C, 78·2; H, 11·8. $C_{21}H_{36}O_2$ requires: C, 78·3; H, 11·8%.)

This diol was also obtained by the hydrogenation of the diol IV (R = H).

The diol IV (R = Me). *A* was reduced in the usual way with LAH in ether to give *the diol* (IV; R = Me) which crystallized from pet. ether as small prisms, m.p. 180-181°; $[\alpha]_D$ +26° (*c*, 2·1). (Found: C, 79·4; H, 10·8. $C_{22}H_{38}O_2$ requires: C, 79·5; H, 10·8%.)

The diol IV (R = H). *B* reduced with LAH in ether as usual gave *the diol* (IV; R = H) as needles (from pet. ether), m.p. 109-110°; $[\alpha]_D$ +18° (*c*, 1·5). (Found: C, 79·5; H, 10·4. $C_{21}H_{34}O_2$ requires: C, 79·3; H, 10·7%.)

The deuteration of A. A solution of *A* (50 mg) in EtOD (5 ml) and D_2O (0·5 ml) containing NaOD (10 mg) was heated under reflux in an atmosphere of N for 30 min. The solvents were then removed *in vacuo*, EtOD (5 ml), D_2O (0·5 ml) and NaOD (10 mg) added, and the mixture refluxed for 30 min. This was repeated 3 times. The mixture was then diluted with D_2O, and the product recovered in ether. It crystallized from pet. ether as prisms, m.p. 149-151°, and was submitted for mass spectrometric analysis. The mol. wt. of 330 indicated the exchange of two hydrogen atoms for deuterium.

The dimerization of (+)-*carvone*. A soln of (+)-carvone (1·8 g) in *t*-butanol (30 ml) containing potassium t-butoxide (from 1·5 g K) was heated under reflux in an atmosphere of N for 3 hr. The initial deep red colour of the soln quickly faded to a pale orange. The mixture was cooled and diluted with water, and the oily product isolated in ether. It was adsorbed on alumina (100 g). Elution with pet. ether–ether (10:4) gave 6,10-*dimethyl*-3,12-*diisopropenyl-tricyclo*-[6.2.2.0^{3,7}]-*dodecana*-5,9-*dione* (VI) as a viscous oil (0·8 g); $[\alpha]_D$ −35° (*c*, 3·3); n_D^{21} 1·5166. IR (film): 1725, 1710, 1645, 893, 890 cm^{-1}. NMR (CDCl$_3$/TMS): 5·10(m), 5·20(m) (2 protons each; −C(CH$_3$)=CH$_2$), 8·31(s), 8·34(s) (3 protons each; —C(CH)=CH$_2$), 8·77, 8·87 (3 protons; J = 6 c/s), 8·90, 9·00 (3 protons; J = 6 c/s) (>CH—CH$_3$) τ. Mol. wt. by mass spectrometry, 300. (Found: C, 79·6; H, 9·7. $C_{20}H_{28}O_2$ requires: C, 80·0; H, 9·3%; mol. wt. 300.)

The dehydration of the diol III (R = H). A soln of the diol III (R = H; 200 mg) in pyridine (5 ml) was treated at 5-10° with a soln of POCl$_3$ (1 ml) in pyridine (3 ml), and the mixture set aside at 5·10° for 12 hr. It was then diluted with ice and the product recovered in ether as an oil. This was adsorbed on alumina (20 g). Elution with pet. ether–benzene (1:1) gave the *olefinic alcohols* (XIV) as an oil (165 mg), $[\alpha]_D$ +45° (*c*, 2·5); n_D^{21} 1·5262. NMR (CCl$_4$/TMS): 4·10-4·40(m) $\left(\underset{|}{-}\text{C—C—H}\right)$, 8·33(s) $\left(-\text{C—C—CH}_3\right)$ τ. IR (Nujol): 3430, 1650 cm^{-1}. (Found: C, 82·5; H, 12·0. $C_{21}H_{34}O$ requires: C, 82·9; H, 11·8%).