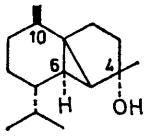
Synthesis of Cubebane-type Sesquiterpenoids and the Stereochemistry of Cubebol [1]

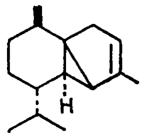
By **Akira Tanaka,** (in part) **Reiko Tanaka, Hisashi Uda,** and **Akira Yoshikoshi,*** Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai, Japan

The total synthesis of cubebane-type sesquiterpenoids, *i.e.* α- and β-cubebenes (II) and (III), and cubebol (I), from (−)-*trans*-caran-2-one (IX), has been accomplished. Pyrolytic cleavage of carane-2-spiro-2′-tetrahydrofuran-5′-one (XII) (having a *trans*-carane structure) led to methyl 3-(*trans*-*p*-mentha-2,8-dien-2-yl)propionate (XV), which was converted into the corresponding diazo-ketone (XVI). Copper-catalysed decomposition of the diazo-ketone resulted in the formation of a mixture of intramolecular addition products, one of which, upon hydrogenation, gave *trans*-7-isopropyl-10-methyltricyclo[4,4,0,$0^{1,6}$]decan-4-one (norcubebanone) (XVIIIa), the key intermediate of this synthesis. Cubebenes and cubebol were synthesised from norcubebanone, and the stereoselective course of the synthesis provided a synthetic proof for the stereochemistry of these sesquiterpenoids.

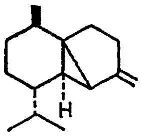
Cubebol, which has long been known by the name of cubebcamphor,[2] is a crystalline sesquiterpene alcohol isolated from the essential oils of the fruits of cubeb (*Piper cubeba* L.) and related plants. Šorm and his co-workers have assigned the structure (I) to cubebol, but have not established the stereochemistry at C-4 and -10.[3] The skeleton of cubebol is a unique modified cadinane with an internal cyclopropane ring. Recently, two olefins related to cubebol, α- and β-cubebene (II) and (III), have been found in the same essential oil[4] and citrus oils,[5] and their structures were elucidated by Hirose and his co-workers.[4,6] The stereochemistry of the methyl groups at C-10 has been assigned by the fact that α-cubebene (II) was transformed into cubenol (IV) and epicubenol (V), whose stereochemistry has been established,[7] by acid-catalysed hydration. These alcohols (IV and V) co-occur with cubebenes in cubeb oil,[7] and a biogenetic relationship between them has been discussed.[6] However no chemical correlation between cubebol and the cubebenes has been reported.



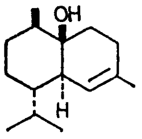
(I)



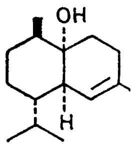
(II)



(III)



(IV)

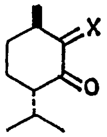


(V)

We have established the stereochemistry of cubebol and achieved the total synthesis of these cubebane-type sesquiterpenoids.

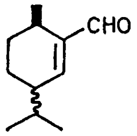
In order to synthesise norcubebanone (XVIIa), which must be a key intermediate for the synthesis of cubebane sesquiterpenoids, intramolecular addition of a keto-carbene, generated from the diazo-ketone (XVI), was projected.[8] Our first step was to extend the formyl group of the unsaturated aldehyde (VII) by two carbon atoms.[†] It was expected that the carboxylic acid (XVa), which may be used for the synthesis of the diazo-ketone (XVI), might be obtained by this route.

The hydroxymethylene-ketone[9] (VIb) derived from (−)-menthone (VIa) was tosylated, then treated with n-butanethiol to give the sulphide (VIc). Some epimerisation of the isopropyl group was observed when (VIb) and (VIc) were formed. The epimerisation was considerable when the sulphide was prepared under acidic conditions. The epimeric mixture of the sulphide was reduced with sodium borohydride, and the resulting alcohols were treated with hydrochloric acid giving an unsaturated aldehyde as an epimeric mixture, along with the sulphide (VIII). The spectra supported the formulation of the aldehyde as the desired compound (VII).

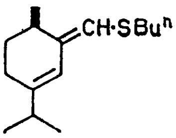


(VI)

a; X = H_2
b; X = CH·OH
c; X = CH·SBu^n



(VII)



(VIII)

When it was found that the aldehyde was obtained as an inseparable mixture of epimers,[‡] we abandoned this

---

[†] This has been accomplished also by Piers *et al.*[8a,b]

[‡] Piers *et al.*[8b] have recently separated the trimethylsilyl ether of alcohols, derived from reduction of the aldehydes, by g.l.c.

[1] Preliminary report, A. Tanaka, H. Uda, and A. Yoshikoshi, *Chem. Comm.*, 1969, 308.

[2] E. Guenther, 'The Essential Oils,' Van Nostrand, New York, 1952, vol. 5, p. 148.

[3] F. Vanášek, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1960, **25**, 919.

[4] Y. Ohta, T. Sakai, and Y. Hirose, *Tetrahedron Letters*, 1966, 6365.

[5] M. K. Veldhuis and G. L. K. Hunter, *J. Food. Sci.*, 1967, **32**, 697.

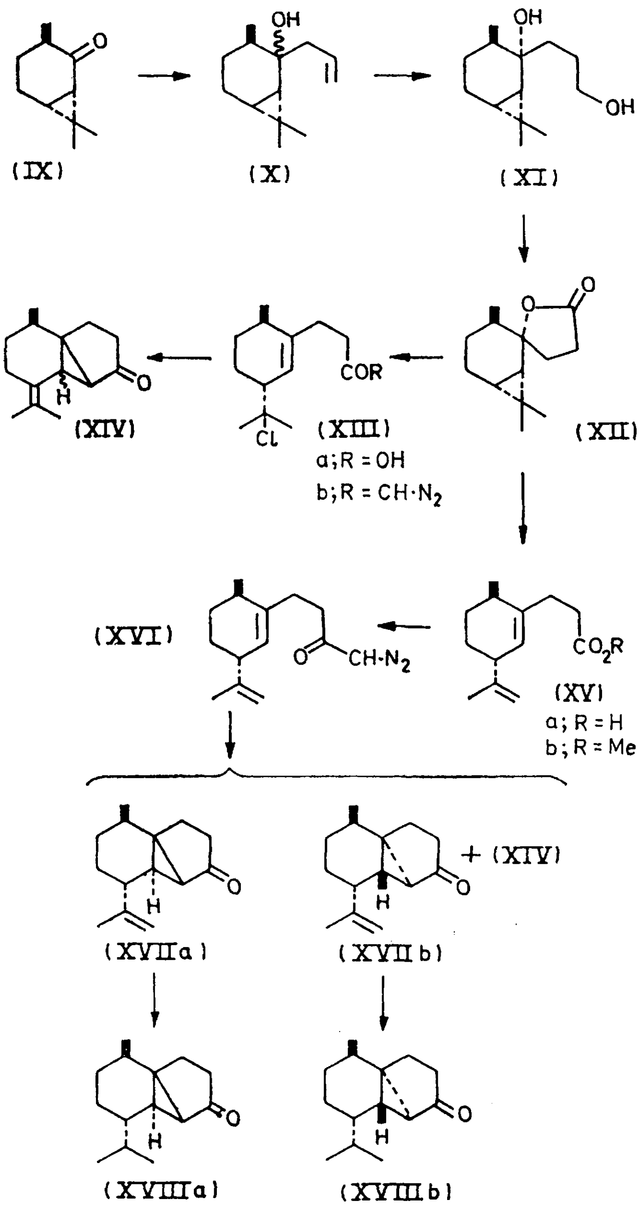
[6] Y. Ohta, K. Ohara, and Y. Hirose, *Tetrahedron Letters*, 1968, 4181.

[7] Y. Ohta and Y. Hirose, *Tetrahedron Letters*, 1967, 2073.

[8] The same key step was examined by other groups, and β-cubebene was synthesised: (*a*) E. Piers, R. W. Britton, and W. de Waal, *Tetrahedron Letters*, 1969, 1251; (*b*) *Canad. J. Chem.*, 1971, **49**, 12; (*c*) O. P. Vig, M. Bhatia, A. K. Verma, and K. L. Matta, *J. Indian Chem. Soc.*, 1970, **47**, 277.

[9] J. Dewar, D. R. Morrison, and J. Read, *J. Chem. Soc.*, 1936, 1598.

route, since the stereochemistry of the 10-methyl group of cubebane sesquiterpenoids was unknown initially. By analogy with the co-occurrence of cubenol (IV) and epicubenol (V) with cubebenes in the same essential oil, we had presumed that cubebane sesquiterpenoids might also possess the same *trans*-menthane moiety as cubenol

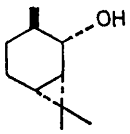


Scheme

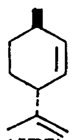
and epicubenol. Thus for our second route, we chose (—)-*trans*-caran-2-one (IX) as the starting material. It has been known that the *trans*-isomer of caran-2-one, unlike methone, is more stable than the *cis*-isomer to base-catalysed equilibration.[10] The cyclopropane ring in the carane system may be cleaved at an appropriate stage of the synthesis, leading to a *trans*-menth-8-ene derivative, *e.g.*, as shown in the step (XII) ⟶ (XV) in the Scheme.

According to the known procedure,[11] (—)-*trans*-caran-2-one (IX) was prepared from (—)-carvone (*p*-mentha-6,8-dien-2-one) as a mixture with the *cis*-isomer (*trans–cis* ratio, *ca.* 4 : 1), and the *trans*-isomer was separated by careful fractional distillation. Allylmagnesium bromide was treated with the caranone (IX) giving a mixture of the alcohols (X), which were sensitive to acids or heat (Scheme). The crude alcohols were submitted to hydroboration–oxidation. From the resulting mixture, one of the products crystallised on standing in 18% yield. Despite the indication of t.l.c. and n.m.r. that this crystalline diol was the major product, separation of additional crystals of the diol from the mother liquor was unsuccessful. Since it has been reported that attack of reagents towards carane derivatives occur selectively in the rear side of the dimethylcyclopropane ring,[10] the major direction of attack of the Grignard reagent in the step (IX) ⟶ (X) would take place in a similar fashion. Accordingly we tentatively assigned the stereochemistry (XI) to the crystalline diol. Chromic anhydride oxidation of the diol (XI) in pyridine gave the spiro-γ-lactone (XII) in good yield.

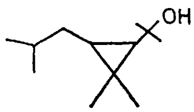
The cleavage of the cyclopropane ring to obtain *trans*-menthane derivatives *via* the spiro-γ-lactone (XII) was examined. The reaction of the spiro-γ-lactone with hydrogen chloride resulted in the formation of the unsaturated chloro-carboxylic acid (XIIIa). Since the product could not be purified owing to its instability, the crude product was treated with oxalyl chloride followed by diazomethane. The crude diazo-ketone thus obtained was heated in boiling cyclohexane in which anhydrous cupric sulphate was suspended, giving a crystalline ketonic product in low yield. The ketone showed a carbonyl absorption at 1705 cm^{-1} and the presence of two olefinic methyl groups in the i.r. and n.m.r. spectra, respectively, and two absorption bands were observed in the u.v. spectrum at 204 and 238 nm. On the basis of these spectral data, the structure (XIV) was tentatively assigned to this ketone. We discontinued further elaboration.



(XIX)



(XX)



(XXI)

Cocker *et al.*[12] have reported the almost selective formation of the non-conjugated diene (XX) on pyrolysis of caran-2-ol (XIX). A similar situation has also been reported for a cyclopropylcarbinol system[13] such as (XXI). The spiro-γ-lactone (XII) was heated with

---

[10] S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, 1967, **89**, 1925.

[11] I. M. Klotz, *J. Amer. Chem. Soc.*, 1944, **66**, 88.

[12] W. Cocker, D. P. Hanna, and P. V. R. Shannon, *J. Chem. Soc.* (*C*), 1968, 489.

[13] L. Crombie, R. R. Houghton, and D. K. Woods, *Tetrahedron Letters*, 1967, 4553.

pyridine in a sealed tube for a short time giving a mixture of unsaturated carboxylic acids. After the product had been treated with diazomethane, g.l.c. analysis indicated that the mixture consisted of 70% of the desired unsaturated ester (XVb) and 30% of five other by-products. The methyl ester (XVb) was separated by preparative g.l.c., and the structure was verified by its spectra.

The unsaturated carboxylic acid (XVa), without purification, was treated with oxalyl chloride followed by diazomethane, whereupon the resulting crude diazoketone was heated with copper powder suspended in boiling cyclohexane. The reaction gave three ketones and the ester (XVb), and each compound was separated by chromatography on alumina followed by preparative g.l.c. The formation of the ester (XVb) is ascribed to part of the acyl chloride being hydrolysed during the operation. The yield of the ketonic products amounted to 25% of the spiro-γ-lactone (XII) used, and the ratio of products was 45 : 36 : 1 (g.l.c.). The least formed ketone was identical with that to which structure (XIV) had been assigned tentatively. Both the two other ketones showed the presence of an exocyclic methylene group and a carbonyl group in conjugation with a cyclopropane ring in their spectra. Therefore, the structures (XVIIa) and (XVIIb) were assigned to these ketones. Both ketones were hydrogenated over tris(triphenylphosphine)rhodium(I) chloride, producing the crystalline ketone (XVIIIa) and the oily ketone (XVIIIb) in quantitative yields, respectively. The oily ketone was derived from the unsaturated ketone most abundantly formed in the ketocarbene addition mentioned before. The u.v. and i.r. spectra of these saturated ketones showed absorptions due to bicyclo[3,1,0]hexan-2-one at 206—207 nm and 1720 cm^{-1}. The stereochemistry of these ketones were investigated by the c.d. spectra.

The Cotton effect associated with the $n \longrightarrow \pi^*$ transition in α-cyclopropylketones followed the 'inverted' octant rule,[14] while Kuriyama *et al.* have shown that the normal octant rule was applicable to the c.d. spectra associated with the $\pi \longrightarrow \pi^*$ transition (200—400 nm) in α-cyclopropylketones.[15]

Figure 1 represents octant projections of both ketones; the octant diagrams lead us to expect that the ketone having the stereoformula (XVIIIa) should show a positive Cotton effect in the $n \longrightarrow \pi^*$ transition region and a negative one in the $\pi \longrightarrow \pi^*$ transition region and that its C-6 epimer should show an antipodal feature. C.d. measurements indicated that the crystalline ketone (XVIIIa) and the oily ketone (XVIIIb) conformed to the former and the latter cases, respectively (Figure 2).

The crystalline ketone showed a m.p. identical with that reported for norcubebanone[4] (XVIIIa), and their identity was proved by comparison of the i.r. and n.m.r. spectra. Since the optical rotation, unfortunately, has not been recorded for norcubebanone, the absolute stereochemistry could not be determined at the present stage. These results were a synthetic proof for the *trans*-menthane stereochemistry of cubebenes.

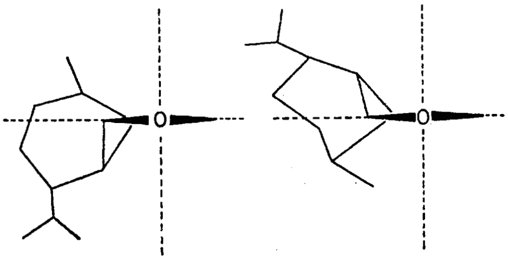


FIGURE 1 Octant projections of norcubebanone (XVIIIa; left) and its C-6 epimer (XVIIIb; right)

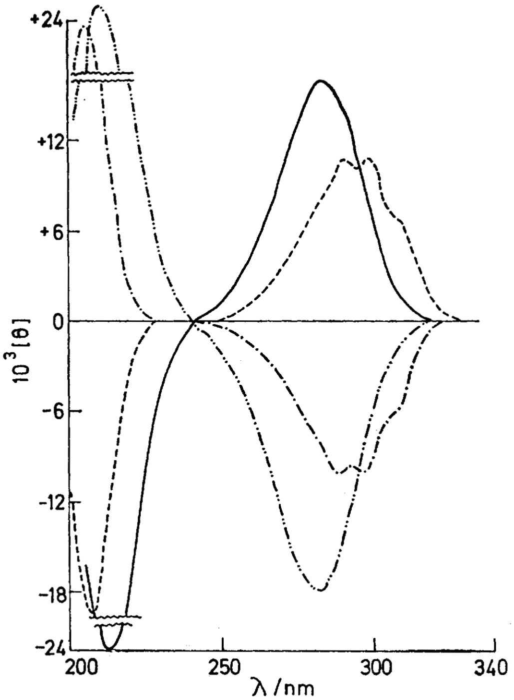


FIGURE 2 C.d. curves of norcubebanone (XVIIIa) and its C-6 epimer (XVIIIb): —— XVIIIa (MeOH); · · · · XVIIIa (iso-octane); —·‧—‧‧— XVIIIb (MeOH); —‧—‧— XVIIIb (iso-octane)

The ketone (XVIIIa) was treated with methylenetriphenylphosphorane to give an olefin in good yield. The olefin was identified as β-cubebene (III) by comparison of the spectra and o.r.d. curves. Similarly, the isomeric ketone (XVIIIb) gave 6-epi-β-cubebene (XXII).

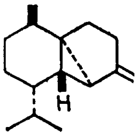
Treatment of the ketone with methyl-lithium or methylmagnesium iodide produced a crystalline alcohol, whose i.r. spectrum was superimposable with that of cubebol (I), and whose optical rotation was the same also. Alkylmetals mainly react at the carbonyl group of the bicyclo[3,1,0]hexan-2-one system on the opposite side to the cyclopropane ring; *e.g.*, sabina ketone (XXIV) gave the alcohol (XXV) by the reaction with methyllithium or methylmagnesium bromide as the major

---

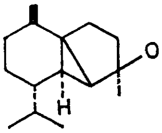
[14] P. Crabbé, 'Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry,' Holden-Day, San Francisco, 1965.

[15] K. Kuriyama, H. Yada, Y. K. Sawa, S. Ito, and I. Itoh, *Tetrahedron Letters*, 1968, 2539.

product.[16] These facts supported the representation of the complete stereochemistry of cubebol by formula (I). For comparison, oxymercuration–demercuration of natural α-cubebene gave an oily alcohol, 4-epicubebol (XXIII). The stereochemistry of (XXIII) at C-4 may be deduced from the known stereochemical course of this reaction.[17] The mass spectra of cubebol and 4-epicubebol showed a similar fragmentation pattern.

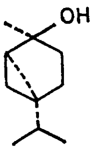


(XXII)



(XXIII)

(XXIV)



(XXV)

Finally, cubebol was dehydrated to α-cubebene. Attempted preparation of a xanthate of cubebol resulted in spontaneous decomposition of the product into a mixture of olefins. The olefinic mixtures consisted of cubebenes and other unidentified olefins, and α-cubebene (II) was separated from the mixture by preparative g.l.c. Dehydration of cubebol by thionyl chloride also gave a similar olefin mixture.

EXPERIMENTAL

All m.p.s and b.p.s are uncorrected. U.v. spectral measurements were made using a Cary model 14 spectrophotometer. I.r. measurements were made using a Hitachi EPI spectrophotometer. N.m.r. spectra with carbon tetrachloride as solvent (unless otherwise stated) and tetramethylsilane as internal standard were taken on a Varian Associate A-60 or T-60 spectrometer, and coupling constants are given in Hz. Mass spectra were obtained with a Hitachi RMU-6D spectrometer. O.r.d. and c.d. measurements were made using a JASCO Model ORD/UV-5 spectropolarimeter.

(−)-p-*Menthan*-3-*one* (*Menthone*) (VIa).—(−)-*p*-Menthan-3-ol [(−)-menthol] was oxidised with sodium dichromate[18] to (−)-*p*-menthan-3-one, $[\alpha]_D$ −25·9° (*c* 5·50 in MeOH) (lit.,[18] $[\alpha]_D$ −29·90°).

Formylation of (−)-p-*Methan*-3-*one*.—Ethyl formate (26 g) was added to a suspension of sodium methoxide [prepared from sodium (8 g) and absolute methanol] in dry benzene (200 ml) at ice-bath temperature, and a solution of (−)-*p*-menthan-3-one [(VIa); 27 g] in dry benzene (50 ml) was then added. After the solution was stirred at room temperature overnight, water was added. The organic layer was washed with 5% sodium hydroxide solution. The combined aqueous layers were acidified with dilute hydrochloric acid and extracted with ether. After evaporating the ether, the residue was distilled *in vacuo* giving 2-hydroxymethylene-*p*-menthan-3-one[9] (VIb) (21·1 g), b.p. 105—107° at 7 mmHg.

2-*n-Butylthiomethylene*-p-*menthan*-3-*one* (VIc).—(*a*) According to the method of Ireland,[19] toluene-*p*-sulphonyl chloride (11·13 g) was dissolved in a stirred solution of the hydroxymethylene-ketone (VIb) (10·68 g) in dry pyridine (43 ml) under nitrogen, in an ice-bath. The solution was stirred for 3 h, then n-butanethiol (10·68 g) was added. After standing in a refrigerator overnight, the mixture was poured into aqueous 0·1N-sodium hydroxide and extracted with ether. The extracts were washed with N-sodium hydroxide. Evaporation gave the crude product, which was distilled *in vacuo* to afford the sulphide (VIc) (4·35 g), b.p. 120—125° at 0·2 mmHg, $\nu_{max.}$ (film) 1662 and 1540 cm^{-1} (Found: C, 70·55; H, 10·5. $C_{15}H_{26}OS$ requires C, 70·85; H, 10·3%). T.l.c. indicated that the sulphide was contaminated with a small amount of the epimer.

(*b*) A solution of the hydroxymethylene-ketone (VIb) (1·0 g), n-butanethiol (1·1 g), and a catalytic amount of toluene-*p*-sulphonic acid in dry benzene (60 ml) was heated under reflux under nitrogen, and the water produced was removed azeotropically. The solution was washed with aqueous sodium hydrogen carbonate solution and dried. The product showed an i.r. spectrum virtually identical with that of the sulphide (VIc) prepared in (*a*), while t.l.c. indicated that the product was contaminated with a larger amount of the epimer.

p-*Menth*-2-*ene*-2-*carbaldehyde* (VII).—A solution of sodium borohydride (1·39 g) in aqueous 0·1N-sodium hydroxide solution (11·6 ml) was added dropwise to a stirred methanolic solution (46 ml) of the sulphide (VIc) (2·31 g), obtained by procedure (*a*), in an ice-bath. After stirring overnight at room temperature, the mixture was diluted with water and extracted with ether. The combined extracts were evaporated to give an oil (2·25 g). The oil was redissolved in ether (60 ml), and hydrochloric acid (3N; 34 ml) was added. The mixture was stirred overnight under nitrogen. After separation, the aqueous layer was extracted twice with ether. The combined ethereal solutions were washed with water and dried. A yellow oil was obtained by evaporation of the solvent and separated on a silica gel column. Light petroleum eluted 2-*n-butylthiomethylene*-p-*menth*-3-*ene* (VIII) (936 mg), b.p. 137° (bath temp.) at 1·1 mmHg, $\lambda_{max.}$ (MeOH) 277 (ε 30,860) and 284 nm (23,500), $\nu_{max.}$ (film) 1570 and 880 cm^{-1}, δ 0·93 and 0·96 (3H, t, *J* 7), 1·02 (6H, d, *J* 7), 2·59 (2H, t, *J* 7), 5·52 (1H, s), and 5·69 p.p.m. (1H, br s) (Found: C, 75·75; H, 10·8. $C_{15}H_{26}S$ requires C, 75·55; H, 11·0%).

Elution with light petroleum–ether gave the unsaturated aldehyde (VII) (520 mg), b.p. 70—75° (bath temp.) at 0·7 mmHg, $\lambda_{max.}$ (MeOH) 232 nm (ε 12,140), $\nu_{max.}$ (film) 2710, 1683, and 1631 cm^{-1} (Found: C, 79·2; H, 10·65. $C_{11}H_{18}O$ requires C, 79·45; H, 10·9%). T.l.c. showed the aldehyde to be a *ca.* 1 : 1 mixture of the epimers, which were observed as closely neighbouring spots.

trans-*Caran*-2-*one* (IX).—*p*-Menth-8-en-2-one [(+)-Dihydrocarvone] (43·3 g) was hydrochlorinated as described by Klotz,[11] and the resulting hydrochloride was dehydrochlorinated with methanolic potassium hydroxide to a mixture of *trans*- and *cis*-caran-2-one. The mixture was carefully fractionally distilled with a spinning band column (70 theoretical plates) giving *trans*-caran-2-one (IX) (20·3 g), b.p. 69° at 2 mmHg. G.l.c. showed that this fraction consisted of 93·5% of the *trans*-isomer and 6·5% of the *cis*-isomer, $[\alpha]_D^{23\cdot5}$ −157·9° (*c* 8·1 in methanol) {lit.,[10] $[\alpha]_D^{26\cdot2}$ −160° (neat)}.

---

[16] J. W. Daly, F. C. Green, and R. H. Eastman, *J. Amer. Chem. Soc.*, 1958, **80**, 6330; W. I. Fanta and W. F. Erman, *J. Org. Chem.*, 1968, **33**, 1656.

[17] H. C. Brown and P. Geoghegan, jun., *J. Amer. Chem. Soc.*, 1967, **89**, 1522; H. C. Brown and W. J. Hammer, *ibid.*, p. 1524; H. C. Brown, J. H. Kawasaki, and S. Ikegami, *ibid.*, p. 1525.

[18] H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, 1961, **83**, 2952.

[19] R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615.

2-(3-*Hydroxypropyl*)*caran*-2-*ol* (XI).—A solution of *trans*-caran-2-one (IX) (61·6 g) in dry ether (150 ml) was added dropwise to a stirred solution of the Grignard reagent [prepared from allyl bromide (160 g) and magnesium (80 g) in ether (1·16 l)] on an ice-bath over a period of 2 h. After stirring overnight at room temperature, water was added, and the organic layer was washed successively with aqueous sodium thiosulphate solution, water, and brine. Evaporation of the solvent left a mixture of the epimers of 2-(prop-2-enyl)caran-2-ol (X), $\nu_{max.}$ (film) 3500, 3080, 1640, 990, and 910 cm^{-1}, which easily decomposed on alumina or silica gel chromatography, or by distilling *in vacuo*. A solution of the crude carbinols in tetrahydrofuran (300 ml) was saturated with diborane in an ice-bath, and the resulting solution was allowed to stand for 7·5 h. The excess of reagent was destroyed with methanol (30 ml). Aqueous sodium hydroxide solution (3N; 150 ml) was added, and the solution was cooled by ice-water. Hydrogen peroxide solution (30%; 150 ml) was added to the stirred solution over a period of 1 h. After standing overnight, the mixture was diluted with water and extracted with ether. The combined extracts were washed with aqueous sodium hydrogen sulphite solution, water, and brine. The extracts gave a semi-solid residue on evaporation. The residue was filtered to obtain crystals, which were recrystallised from acetone giving the pure diol (XI) (15·6 g; 18%) as plates, m.p. 143—145°, $\nu_{max.}$ (KBr) 3300 and 1075 cm^{-1}, δ (pyridine) 1·03 (3H, s), 1·03 (3H, d, *J* 7), 1·07 (3H, s), and 3·95 p.p.m. (2H, t, *J* 6) (Found: C, 73·65; H, 11·0. $C_{13}H_{24}O_2$ requires C, 73·55; H, 11·35%).

Since t.l.c. and the n.m.r. spectrum of the crude mixture showed that the diol appeared to be the most abundant product, separation of the additional diol from the mother liquor was attempted using a neutral alumina column. The separation was unsuccessful.

Oxidation of the Diol (XI) *with Chromic Acid*.—The Sarett reagent [prepared from chromic anhydride (1·1 g) and dry pyridine (10 ml)] was added to a solution of the diol (XI) (400 mg) in dry pyridine (5 ml). The solution was stirred at room temperature overnight. Ether was added, and the solution was filtered. After work-up of the filtrate, the crude product was distilled *in vacuo*, b.p. 120—125° (bath temp.) at 2 mmHg, affording *carane*-2-*spiro*-2′-*tetrahydrofuran*-5′-*one* (XII) (350 mg; 89%). The distillate crystallised on standing, and an analytical sample was obtained as leaflets, m.p. 57—59° (from n-hexane), $\nu_{max.}$ (KBr) 1775 cm^{-1} (Found: C, 75·1; H, 9·6. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%).

7-*Isopropylidene*-10-*methyltricyclo*[4,4,0,$0^{1,5}$]*decan*-4-*one* (XIV).—A solution of the spiro-γ-lactone (XII) (100 mg) in dry ether (6 ml) at ice-bath temperature was saturated with dry hydrogen chloride. After standing for 15 min, the solution was washed with water. Evaporation left the crude 3-(*trans*-8-chloro-*p*-menth-2-en-2-yl)propionic acid (XIIIa) (100 mg), $\nu_{max.}$ (film) 1710 cm^{-1}, δ ($CDCl_3$) 1·00 (3H, d, *J* 6), 1·47 (3H, s), 1·55 (3H, s), 2·40 (4H, s), 5·55 (1H, br s), and 9·64 p.p.m. (1H, br s).

The crude product was treated with diazomethane to give methyl ester. Attempted purification of the ester on a silica gel column was unsuccessful, because decomposition (probably dehydrochlorination) occurred.

A solution of the crude chloro-carboxylic acid (XIIIa) (378 mg) and pyridine (2 drops) in dry benzene was cooled in an ice-bath, and oxalyl chloride (0·7 ml) was added dropwise. After additional stirring for 1 h at room temperature, the solvent was eliminated *in vacuo* giving an acyl chloride, $\nu_{max.}$ (film) 1800 cm^{-1}. The acyl chloride was treated with an excess of ethereal diazomethane, and evaporation left the crude diazo-ketone (XIIIb), $\nu_{max.}$ (film) 2100 and 1640 cm^{-1}. A solution of the diazo-ketone in dry cyclohexane (50 ml) was added to a suspension of anhydrous copper(II) sulphate (0·3 g) in boiling cyclohexane (50 ml) during 1 h. Reflux was continued for additional 1 h. The mixture was filtered and evaporated. The residue, a complex mixture of products (t.l.c.), was chromatographed on a neutral alumina column, and crystals were eluted by light petroleum–ether (50 : 1). Recrystallisation of the crystals from n-hexane followed by sublimation *in vacuo* gave the pure *ketone* (XIV) (7 mg), m.p. 83—84°, $\lambda_{max.}$ (MeOH) 204 (ε 13,300) and 238 nm (7920), $\nu_{max.}$ (KBr) 1705 cm^{-1}, δ 1·08 (3H, d, *J* 7), 1·58 (3H, s), 1·68 (3H, s), and 1·93 p.p.m. (6H, s) (Found: C, 75·35; H, 9·85. $C_{14}H_{22}O_2$ requires C, 75·65; H, 9·95%).

Pyrolysis of the Spiro-γ-lactone (XII).—A mixture of the spiro-γ-lactone (XII) (0·50 g) and pyridine (0·4 ml) was heated in a sealed tube at 250—300° for 5 min. Elimination of the pyridine *in vacuo* left a mixture of unsaturated carboxylic acids, which was then treated with diazomethane. G.l.c. (column, 20% PEG 20M, 3 mm × 2·5 m; 162°) of the product showed six peaks, the largest one of which formed 70% of the total area of the peaks. The major product, *methyl* 3-(trans-p-*mentha*-2,8-*dien*-2-*yl*)*propionate* (XVb), was separated by preparative g.l.c., $\nu_{max.}$ ($CHCl_3$) 1730, 1643, and 895 cm^{-1}, δ 1·03 (3H, d, *J* 6), 1·65 (3H, d, *J* 1), 3·54 (3H, s), 4·60 (2H, m), and 5·22 p.p.m. (1H, br s) (Found: C, 75·35; H, 9·85. $C_{14}H_{22}O_2$ requires C, 75·65; H, 9·95%).

Pyrolysis of the spiro-γ-lactone alone gave a more complex mixture of carboxylic acids, which showed n.m.r. signals in aromatic proton region.

The Epimers of 7-*Isopropenyl*-10-*methyltricyclo*[4,4,0,$0^{1,5}$]-*decan*-4-*one*, (XVIIa) *and* (XVIIb).—The crude mixture of the carboxylic acids (XV) obtained upon pyrolysis of the spiro-γ-lactone (XII) (1·5 g) was dissolved in dry benzene containing pyridine (1 ml). Oxalyl chloride (2 ml) was added to the stirred solution in an ice-bath. Stirring was continued for 1 h at the same temperature and for additional 30 min at room temperature. The mixture was filtered, and the solvent was removed by evaporation *in vacuo*. The residue was treated with an excess of ethereal diazomethane giving the crude diazo-ketone (XVI), $\nu_{max.}$ (film) 2200, 1635, and 885 cm^{-1}. A cyclohexane solution (150 ml) of the diazo-ketone was added dropwise to a stirred suspension of copper powder (0·5 g) in boiling cyclohexane (150 ml) during 1 h. Reflux was continued for additional 1 h, and the mixture was cooled and filtered. The product, obtained on evaporation, showed four g.l.c. peaks (column, 20% PEG 20M, 3 mm × 2·5 m; 212°; helium flow, 40 ml min^{-1}) at retention times R_t of 3·5, 6·9, 9·3, and 10·0 min. The ratio was 4 : 5 for the peaks of 6·9 and 9·3 min, which corresponded to the ketones (XVIIa) and (XVIIb), respectively, as will be mentioned later. The above mixture chromatographed on a neutral alumina column; light petroleum–ether (50 : 1) eluted the unsaturated ester (XVb) (220 mg), which was identified by i.r. and g.l.c. (R_t 3·5 min). Elution with light petroleum–ether (20 : 1) gave a mixture of three ketones (560 mg) and the pure *ketone* (XVIIb) (100 mg), $\lambda_{max.}$ (MeOH) 204 nm (ε 7220), $\nu_{max.}$ ($CHCl_3$) 1708, 1645, and 895 cm^{-1}, δ 1·09 (3H, d, *J* 7), 1·66 (3H, s), and 4·62 p.p.m. (2H, s), c.d. (*c* 0·35 in MeOH) $[\theta]_{214}$ +23,900 (peak), $[\theta]_{240}$ 0, and $[\theta]_{282}$ −23,400 (trough),

$[\alpha]_D$ −16·8° (Found: C, 82·2; H, 10·05. $C_{14}H_2$ O requires C, 82·3; H, 9·85%). The ketone showed a single peak in g.l.c. with R_t 9·3 min.

The ketonic mixture, obtained by chromatography, was separated by preparative g.l.c. giving an additional amount (145 mg) of (XVIIb), the ketone (XIV) (15 mg; R_t 10·0 min; identified by i.r.), and the *ketone* (XVIIa) (105 mg; R_t 6·9 min), $\lambda_{max.}$ (MeOH) 205 nm (ε 7950), $\nu_{max.}$ ($CHCl_3$) 1708, 1650sh, and 895 cm^{-1}, δ ($CHCl_3$) 1·00 (3H, d, *J* 6), 1·77 (3H, s), and 4·70 p.p.m. (2H, s), c.d. (*c* 0·37 in MeOH) $[\theta]_{215}$ −24,100 (trough), $[\theta]_{240}$ 0, and $[\theta]_{284}$ +14,200 (peak), $[\alpha]_D$ −42·6° (Found: C, 81·95; H, 9·95. $C_{14}H_{20}O$ requires C, 82·3; H, 9·85%).

Hydrogenation of the Ketones (XVIIa *and* XVIIb).—(*a*) A solution of the ketone (XVIIa) (70 mg) and tris(triphenylphosphine)rhodium(I) chloride [20] (50 mg) in benzene (10 ml) was hydrogenated under atmospheric pressure at room temperature. The mixture was passed through a short neutral alumina column to remove the catalyst. Evaporation gave *trans*-7-isopropyl-10-methyltricyclo[4,4,0,0^{1,5}]decan-4-one (norcubebanone) (XVIIIa) (68 mg), which crystallised on standing. Recrystallisation from light petroleum gave an analytical sample, m.p. 57—58° (lit.,[4] 58·5—59·5°), $\lambda_{max.}$ (MeOH) 206 nm (ε 6200) (lit.,[4] $\lambda_{max.}$ 209 nm), $\nu_{max.}$ (CCl_4) 1723 cm^{-1} (lit.,[4] $\nu_{max.}$ 1715 cm^{-1}), δ 0·90, 0·92, and 1·00 p.p.m. (3H, d, *J* 6 each), c.d. (*c* 0·16 in MeOH), $[\theta]_{283}$ +15,910 (peak) and $[\theta]_{213}$ −23,650 (trough), $[\alpha]_D$ −23·9°; (*c* 0·11 in iso-octane) $[\theta]_{297\cdot5}$ +10,700, $[\theta]_{290}$ +10,600, and $[\theta]_{207}$ −19,400, $[\alpha]_D$ −38·7° (Found: C, 81·75; H, 10·55. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%). The i.r. and mass spectra of this ketone were identical with those of norcubebanone derived from natural β-cubebene

(*b*) By a similar treatment the ketone (XVIIa) (100 mg) gave the oily epimeric *saturated ketone* (XVIIIb) (98 mg), $\lambda_{max.}$ (MeOH) 207 nm (ε 6760), $\nu_{max.}$ (CCl_4) 1723 cm^{-1}, δ 0·83 and 0·91 (3H, d, *J* 5), and 1·0 p.p.m. (3H, d, *J* 7), c.d. (*c* 0·37 in MeOH) $[\theta]_{282}$ −18,100 and $[\theta]_{210}$ +24,000, $[\alpha]_D$ −2·4°; (*c* 0·39 in iso-octane) $[\theta]_{297}$ −10,200, $[\theta]_{289}$ −10,200, and $[\theta]_{205}$ +22,600, $[\alpha]_D$ +3·6° (Found: C, 81·4; H, 10·65. $C_{14}H_{22}O$ requires C, 81·5; H, 10·75%).

7-*Isopropyl*-10-*methyl*-4-*methylenetricyclo*[4,4,0,0^{1,5}]*decane* (β-*Cubebene*) (III).—A solution of norcubebanone (XVIIIa) (103 mg) in dimethyl sulphoxide (2 ml) was added to a methylenetriphenylphosphorane solution [prepared from methyltriphenylphosphonium bromide (240 mg), sodium hydride (240 mg), and dimethyl sulphoxide (7 ml)]. After the solution was heated at 50—60° for 24 h, an ylide solution newly prepared from the phosphonium salt (120 mg) was added. Heating was continued for an additional 66 h. The mixture was poured into water and extracted with pentane. Work-up followed by distillation gave β-*cubebene* (III) (79 mg), $\lambda_{max.}$ (MeOH) 208 nm (ε 9300), $\nu_{max.}$ (film) 3080, 1650, and 860 cm^{-1}, δ 0·90 (3H, d, *J* 6), 0·93 (6H, d *J* 6), 4·50 (1H, br s), and 4·70 p.p.m. (1H, br s), o.r.d. (*c* 0·15 in MeOH), a positive plane curve, $[\phi]_{204}$ +7000°, $[\phi]_{285}$ 0°, and $[\phi]_{350}$ −600°, $[\alpha]_D$ −72·3°, M^+, 204 (Found: C, 88·15; H, 11·35. $C_{15}H_{24}$ requires C, 88·15; H, 11·85%). The i.r., n.m.r., and mass spectra, and o.r.d. of a sample were identical with those of natural β-cubebene.

6-*Epi*-β-*cubebene* (7α-*Isopropyl*-10β-*methyl*-4-*methylene*-6β-*tricyclo*[4,4,0,0^{1,5}]*decane*) (XXII).—The saturated ketone (XVIIIb) (412 mg) was treated with methylenetriphenylphosphorane in the same manner as described for the preparation of β-cubebene. Work-up gave 6-*epi*-β-*cubebene* (XXII) (387 mg), $\lambda_{max.}$ (MeOH) 209 nm (ε 11,500), $\nu_{max.}$ (film) 3080, 1650, and 860 cm^{-1}, δ 0·93 (3H, d, *J* 4), 1·07 (6H, d, *J* 7), 4·57 (1H, br s), and 4·73 p.p.m. (1H, br s), o.r.d. (*c* 0·44 in MeOH), a negative plain curve, $[\phi]_{250}$ −1000°, $[\phi]_{263}$ 0°, and $[\phi]_{300}$ +450°, $[\alpha]_D$ +78·8° (Found: C, 87·6; H, 11·4. $C_{15}H_{24}$ requires C, 88·15; H, 11·85%).

Cubebol (7α-*Isopropyl*-4β,10β-*dimethyl*-6α-*tricyclo*-[4,4,0,0^{1,5}]*decan*-4α-*ol*) (I).—To the Grignard reagent [prepared from methyl iodide (520 mg), magnesium (88 mg), and dry ether (6 ml)] was added dropwise a solution of norcubebanone (XVIIIa) (150 mg) in dry ether (3 ml) in an ice-bath. The mixture was heated under reflux for 3 h and the excess of reagent was destroyed by adding water. Work-up of the organic layer gave a crystalline product, which was recrystallised from light petroleum giving cubebol (I) (70 mg), which was identified by i.r. T.l.c. indicated that the crude product consisted mainly of cubebol. An analytical sample was obtained by sublimation as prisms, m.p. 61—62°, $[\alpha]_D^{20}$ −48·3° (*c* 3·52 in $CHCl_3$) (lit.,[3] m.p. 64°, $[\alpha]_D^{20}$ −61·6°), $\nu_{max.}$ (CCl_4) 3700 and 3450 cm^{-1}, δ ($CDCl_3$) 0·90 (6H, d, *J* 7), 0·95 (3H, d, *J* 6), and 1·27 p.p.m. (3H, s), *m*/*e* 204 (M^+ − H_2O) and 161 (base peak) (Found: C, 80·8; H, 11·55. $C_{15}H_{26}O_2$ requires C, 81·0; H, 11·8%). The reaction of norcubebanone with methyl-lithium gave similar results.

4-*Epicubebol*.—A solution of natural α-cubebene (II) (70 mg) was added to a stirred suspension of mercury(II) acetate (109 mg) in 50% aqueous tetrahydrofuran solution (2 ml), after the method of Brown.[17] After the solution was stirred for 15 min, sodium hydroxide solution (3N; 1 ml) and a 3N-sodium hydroxide solution of sodium borohydride (0·5M, 1 ml) was added. The mixture was saturated with sodium chloride, and the organic layer was separated. The aqueous layer was extracted with tetrahydrofuran. The solvent was removed from the combined tetrahydrofuran solution, and the residue was chromatographed on an alumina column. Light petroleum eluted an oily alcohol, 4-*epicubebol* (XXIII) (23 mg). An analytical sample was obtained by distillation, $\nu_{max.}$ (CCl_4) 3600 and 3450 cm^{-1}, δ ($CDCl_3$) 0·83 (3H, d, *J* 6), 0·93 (3H, d, *J* 7), and 1·33 p.p.m. (3H, s), *m*/*e* 204 (M^+ − H_2O) and 161 (base peak) (Found: C, 81·1; H, 10·95. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%).

Chugaev Reaction of Cubebol.—According to the method of Corey,[21] a solution of cubebol (54 mg) in dimethyl sulphoxide (1 ml) was added to a methylsulphinyl carbanion solution [prepared from sodium hydride (16 mg) and dimethyl sulphoxide (1 ml)] and the mixture was stirred for 30 min. A solution of carbon disulphide (26 mg) in ether (1 ml) was added. The resulting deep red solution was left for 30 min. Methyl iodide (48 mg) dissolved in ether (1 ml) was added, and the solution was stirred for 3 h at room temperature. The solution was poured onto ice–water and extracted with ether. Work-up gave a yellow oil. G.l.c. showed that the oil contained α- and β-cubebenes (1 : 2), and other hydrocarbons. A small amount of α-cubebene, $\nu_{max.}$ (film) 1645, 825, and 778 cm^{-1}, was isolated from the mixture by preparative g.l.c., and identified by comparison of the i.r. and mass spectra with those of the natural product (*M*, 204·1864. Calc. for $C_{15}H_{24}$: *M*, 204·1873).*

---

* High resolution mass spectra were taken with a JEOL JMS-O15 G mass spectrometer by courtesy of Japan Electron Optics Laboratory, which we gratefully acknowledge.

[20] J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc.* (*A*), 1966, 1711.

[21] E. J. Corey and H. Uda, *J. Amer. Chem. Soc.*, 1963, **85**, 1788.

Dehydration of Cubebol by Thionyl Chloride.—A solution of the crude cubebol (20 mg) and pyridine (0·5 ml) in dichloromethane (2 ml) was treated with thionyl chloride at −30° for 5 min. The mixture was poured onto ice–water and extracted with dichloromethane. G.l.c. of the residue, obtained by evaporating the solvent from the extracts, showed that the product consisted of cubebenes (α : β, *ca.* 1 : 2) and other hydrocarbons.

We thank Dr. Y. Hirose for providing authentic samples of cubebenes, Mr. Y. Ueno for supplying (−)-carvone and (−)-menthol, Professor V. Herout and Drs. Y. Hirose and G. L. K. Hunter for identification of cubebol, norcubebanone, and cubebenes, respectively, and Dr. K. Kuriyama for o.r.d. and c.d. measurements.

[1/2384 *Received*, 13*th December*, 1971]