412. *Sesquiterpenoids. Part II.* Tricyclic Derivatives of Caryophyllene.*

By D. H. R. Barton, T. Bruun, and A. S. Lindsey.

The dicarboxylic acid $C_{12}H_{18}O_4$ obtained previously * from caryophyllene has been shown to be a ditertiary acid. Caryophyllene itself must, therefore, be formulated as 4 : 11 : 11-trimethyl-8-methylene*bicyclo*[7 : 2 : 0]undec-4-ene.

The compound $C_{15}H_{26}O_2$ formed as a by-product of the action of hydrogen peroxide on caryophyllene has been shown to be a saturated tricyclic secondary-tertiary glycol. Removal of the secondary hydroxyl group afforded β-caryophyllene alcohol. Stepwise degradation of the glycol $C_{15}H_{26}O_2$ by several different routes gave a keto-acid $C_{13}H_{20}O_3$ formulated as 2-keto-4 : 8 : 8-trimethyl*bicyclo*[5 : 2 : 0]nonane-4-carboxylic acid. This formulation shows that the glycol $C_{15}H_{26}O_2$ and β-caryophyllene alcohol must be represented as 1 : 9-dihydroxy- and as 1-hydroxy-4 : 4 : 8-trimethyl*tricyclo*-[6 : 3 : 1 : $0^{2,5}$]dodecane, respectively.

The chloride formed by the action of phosphorus pentachloride on β-caryophyllene alcohol is formulated as 1-chloro-4 : 4 : 8-trimethyl*tricyclo*-[6 : 3 : 1 : $0^{2,5}$]dodecane, on the basis of the stepwise degradation of the corresponding chloro-compound from the monoacetate of the glycol $C_{15}H_{26}O_2$.

The absence of an α-hydrogen atom in clovenic acid, combined with the degradational evidence reported above, implies that clovene should probably be formulated as 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]dodec-2-ene.

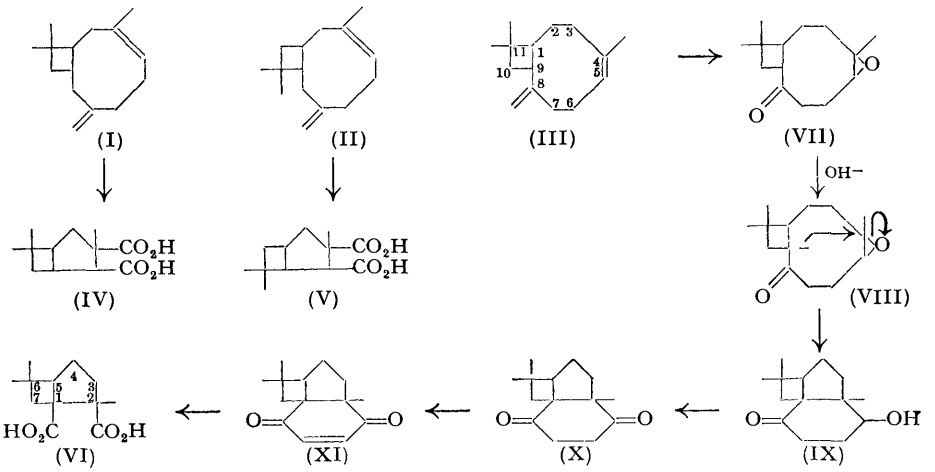
The stereochemistry of caryophyllene and some of its derivatives is briefly discussed.

Comment is made on anomalies in the absorption spectra of some saturated 2 : 4-dinitrophenylhydrazones.

The results reported in Part I* of this series restricted the number of possible formulæ for caryophyllene to three (I), (II), and (III). A decision in favour of (III) has been reached by a study of the properties of the dicarboxylic acid $C_{12}H_{18}O_4$ obtained previously by stepwise degradation. The possible formulæ for this acid are (IV), (V), and (VI). Both (IV) and (V) are secondary-tertiary dicarboxylic acids whereas (VI) is ditertiary. All

* Part I, *J.*, 1951, 2988. Most of the results reported in the present paper were summarised in a preliminary communication (Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1951, 910).

attempts to brominate the dicarboxylic acid (as its anhydride) failed owing to lack of reactivity. The anhydride was not isomerised by acetic anhydride at 220° (test for a *trans*-anhydride with at least one α-hydrogen atom), nor was the acid isomerised by con-



centrated hydrochloric acid at 180° (test for a *cis*-dicarboxylic acid with at least one α-hydrogen atom). The dimethyl ester of the acid was resistant to alkaline hydrolysis. All these properties are in best accord with the formulation of the dicarboxylic acid $C_{12}H_{18}O_4$ as 2 : 6 : 6-trimethyl*bicyclo*[3 : 2 : 0]heptane-1 : 2-dicarboxylic acid (VI), and we conclude therefore that caryophyllene is correctly regarded as 4 : 11 : 11-trimethyl-8-methylene-*bicyclo*[7 : 2 : 0]undec-4-ene (III). The degradational sequence described in Part I must now be formulated as indicated, (VII) ⟶ (VIII) ⟶ (IX) ⟶ (X) ⟶ (XI) ⟶ (VI). In agreement, the dione (XI), with no α-hydrogen atom, was resistant to bromination even under vigorous conditions. Previously we had reported (Part I, *loc. cit.*) that both (IX) and (X) formed mono-2 : 4-dinitrophenylhydrazones. Under rather more vigorous reaction conditions a bis-2 : 4-dinitrophenylhydrazone has now been obtained from (X).

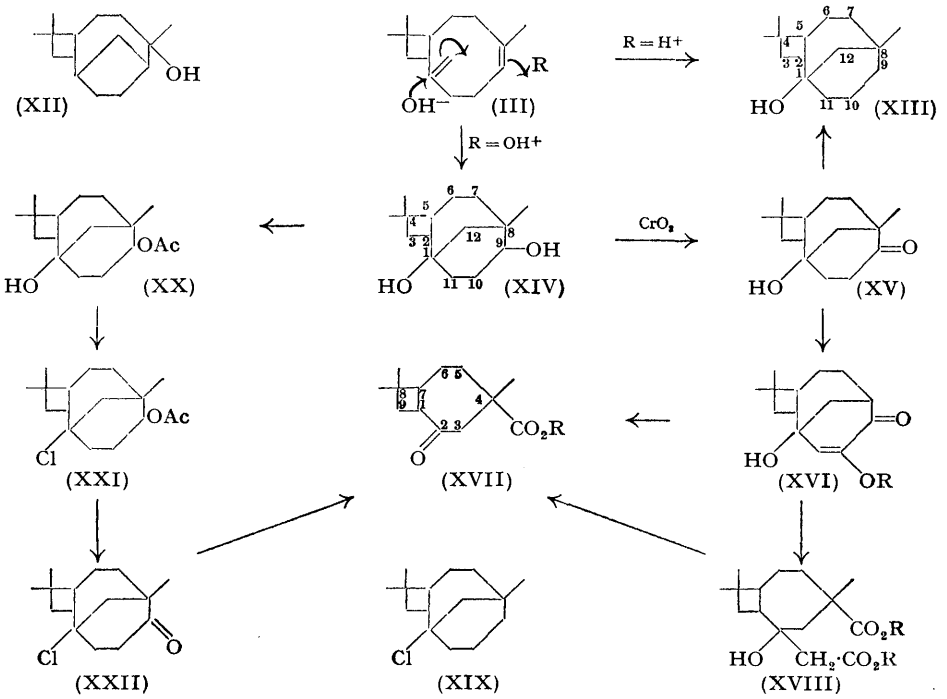
One of the outstanding characteristics of the caryophyllene molecule is its facile cyclisation under acid conditions to tricyclic compounds (for summary see Simonsen and Barton, " The Terpenes," Vol. III, Cambridge Univ. Press). The most important cyclisation products are α- and β-caryophyllene alcohol, $C_{15}H_{26}O$, and the hydrocarbon clovene, $C_{15}H_{24}$. A further tricyclic caryophyllene derivative was recognised, during our work, in the crystalline glycol, $C_{15}H_{26}O_2$, m. p. 107°, $[\alpha]_D$ −5°, obtained as a by-product of the action of hydrogen peroxide on caryophyllene (Treibs, *Chem. Ber.*, 1947, **80**, 56). This glycol was shown to be saturated, for it gave no colour with tetranitromethane and exhibited no absorption in the far ultra-violet. Acetic anhydride in pyridine at room temperature gave a crystalline monoacetate, whilst chromic acid furnished a crystalline monohydroxy-ketone which was resistant to further oxidation. We conclude that the glycol contains one secondary and one tertiary hydroxyl group. Reduction of the hydroxy-ketone by the Wolff–Kishner method afforded β-caryophyllene alcohol. This tertiary alcohol has been prepared from caryophyllene under a variety of acid hydrating conditions. The mildest of these would appear to be the action of formic acid (Robertson, Kerr, and Henderson, *J.*, 1925, 1944; Henderson, Robertson, and Kerr, *J.*, 1926, 62), which gives the formate. If the formation of four-membered rings, and the migration of double bonds prior to cyclisation, are excluded, then there are only two formulæ, (XII) and (XIII), which can be derived for β-caryophyllene alcohol. Of these (XIII) appears the more probable since it involves only Markownikoff addition. Its correctness was shown by the reactions outlined in the sequel.

It seemed likely that the glycol $C_{15}H_{26}O_2$, with its two functional groups available as initial points for stepwise degradation, would prove a valuable compound in establishing a formula for β-caryophyllene alcohol. If the formation of the glycol is regarded as electro-

philic attack by OH^+ then it is possible, on the basis of formula (XIII) for β-caryophyllene alcohol, to write a common mechanism of genesis (see formulæ) for both the glycol (XIV) and the β-alcohol. These theoretical views were confirmed by the following evidence.

Oxidation of the keto-alcohol (XV), prepared as mentioned above, with selenium dioxide gave a crystalline diosphenol (XVI; R = H), further characterised as the crystalline acetate. Oxidation of this acetate by potassium permanganate in acetone solution gave a liquid keto-acid $C_{13}H_{20}O_3$ characterised as the crystalline methyl ester 2 : 4-dinitrophenylhydrazone. We formulate this keto-acid as 2-keto-4 : 8 : 8-trimethyl*bicyclo*[5 : 2 : 0]-nonane-4-carboxylic acid (XVII; R = H). Its formation proves the presence of the grouping $-CH(OH)\cdot CH_2\cdot CH_2\cdot C(OH)<$ in the glycol $C_{15}H_{26}O_2$ and hence of the grouping $-[CH_2]_3\cdot C(OH)<$ in β-caryophyllene alcohol. The keto-acid $C_{13}H_{20}O_3$ was also obtained in the following ways. Oxidation of the diosphenol (XVI; R = H) with cold alkaline hydrogen peroxide furnished an acid (XVIII; R = H) which could not be crystallised. The derived dimethyl ester was also non-crystalline and on dehydration with phosphorus oxychloride in pyridine at room temperature gave a mixture of unsaturated esters in which an αβ-unsaturated ester ($\lambda_{max.}$ 224 mμ, ε = 3000) was present to a probable extent of about 25%. Ozonolysis of the mixed esters gave the methyl ester of the keto-acid $C_{13}H_{20}O_3$, again characterised as the 2 : 4-dinitrophenylhydrazone. The most efficient method for the production of the keto-acid $C_{13}H_{20}O_3$ was found to be heating (XVIII; R = H) with 50% aqueous potassium hydroxide.

The formulation of the keto-acid $C_{13}H_{20}O_3$ is also supported by the following evidence. It is not a β-keto-acid as it is not readily decarboxylated. The carboxyl group of (XVII;

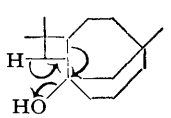


R = H) is subject to marked steric hindrance which is in accordance with the formula assigned. Evidence was obtained that, as in formula (XVII; R = H), the keto-group was adjacent to an enolisable asymmetric centre: thus, when the keto-acid (XVII; R = H) was obtained by permanganate oxidation of (XVI; R = Ac), or by the action of concentrated alkali on (XVIII; R = H), it was accompanied by a stereoisomer, characterised as the crystalline methyl ester 2 : 4-dinitrophenylhydrazone. The two compounds, as the methyl ester 2 : 4-dinitrophenylhydrazones, could be equilibrated by hydrochloric–acetic

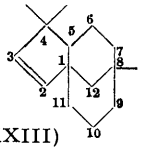
acid. The lower-melting isomer (m. p. 169—170°), which was appreciably more stable, is regarded as having the *cyclo*butane ring fused *cis*, and the higher-melting isomer (m. p. 184·5—185·5°) is considered to be the *trans*-form. The keto-acid $C_{13}H_{20}O_3$ was *not* a methyl ketone for it was recovered unchanged, on treatment with alkaline hypoiodite. The accumulation of evidence reinforces the correctness of the formulation of the glycol $C_{15}H_{26}O_2$ and of β-caryophyllene alcohol as 1 : 9-dihydroxy- and 1-hydroxy-4 : 4 : 8-trimethyl-*tricyclo*[6 : 3 : 1 : $0^{2,5}$]dodecane, (XIV) and (XIII) respectively.

Considerable theoretical interest attaches to the replacement reactions of bicyclic compounds with substituents at the bridge-head (see, for example, Bartlett, *Colloques Internationaux, Réarrangements Moléculaires et Inversion de Walden*, Montpelier, 1950, p. 108). β-Caryophyllene alcohol (XIII) is now seen to be a compound of this type although, as a 1-hydroxy-derivative of *bicyclo*[4 : 3 : 1]nonane, it contains a ring system which appears to be novel. Wallach and Walker (*Annalen*, 1892, **271**, 288) first noted that β-caryophyllene alcohol, on treatment with phosphorus pentachloride, gave very smoothly a highly crystalline chloride, $C_{15}H_{25}Cl$. Later Henderson, Robertson, and Kerr (*loc. cit.*) observed that this chloride was resistant to nucleophilic reagents, although it reacted with sodium acetate in acetic acid to furnish the acetate of β-caryophyllene alcohol. It must be concluded that, either the chloride has the formula (XIX) and undergoes replacement without rearrangement, or that rearrangement is involved both in the genesis of the chloride and in its reconversion into β-caryophyllene alcohol. These problems were answered by a further study of the reactions of the $C_{15}H_{26}O_2$ glycol (XIV). When the monoacetate (XX) was treated with phosphorus pentachloride it reacted smoothly to give a highly crystalline chloroacetate, $C_{17}H_{27}O_2Cl$, in almost quantitative yield. This compound must be formulated as (XXI), for on alkaline hydrolysis followed by chromic acid oxidation it gave a crystalline chloro-ketone (XXII). This was treated successively with selenium dioxide (to give the diosphenol), alkaline hydrogen peroxide (to give the dicarboxylic acid), and 50% aqueous potassium hydroxide (to cause dehydrochlorination and subsequent cleavage of the αβ-unsaturated acid), thus yielding the keto-acid $C_{13}H_{20}O_3$ (XVII; R = H), characterised as before as the methyl ester 2 : 4-dinitrophenylhydrazone. We conclude that replacement of the tertiary hydroxyl group by chlorine occurs without rearrangement of the carbon skeleton and with retention of stereochemical configuration. The chloride from β-caryophyllene alcohol is, therefore, correctly formulated as (XIX). It appears that there is sufficient flexibility in the ring system of β-caryophyllene alcohol to allow formation of an essentially planar carbonium ion at the bridgehead.

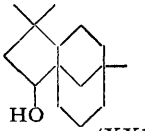
When β-caryophyllene alcohol is dehydrated by boiling it with phosphoric oxide (Wallach and Walker, *loc. cit.*; Henderson, McCrone, and Robertson, *J.*, 1929, 1368) it affords the tricyclic hydrocarbon clovene. The latter is peculiar in that it contains the grouping $\geqslant C{\cdot}CH{:}CH{\cdot}C\leqslant$ and affords on oxidation crystalline clovenic acid, $C_{15}H_{24}O_4$. This acid readily forms an anhydride, but resists bromination and ketonisation (Ruzicka and Gibson, *Helv. Chim. Acta*, 1931, **14**, 570). We have confirmed the absence of α-hydrogen atoms by showing that (*a*) clovenic acid is not isomerised by concentrated hydrochloric acid at 180° and (*b*) clovenic acid anhydride is not isomerised by acetic anhydride at 220°. It can be concluded that the double bond of clovene is contained in a five-membered ring and is



(XIII)



(XXIII)



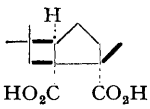
(XXIV)

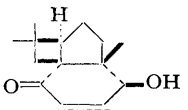
placed between two quaternary carbon atoms. The simplest derivation of such a system from β-caryophyllene alcohol (XIII) would appear to be as indicated, thus giving clovene the formula (XXIII) (4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1,5}$]dodec-2-ene).

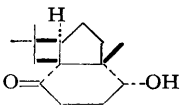
α-Caryophyllene alcohol, which is formed together with the β-isomer by acid-catalysed hydration, is simply related to clovene. Thus it gives clovenic acid on oxidation (Bell and Henderson, *J.*, 1930, 1971); it must, therefore, be a secondary alcohol, presumably (XXIV).

On dehydration with phosphoric oxide or oxalic acid α-caryophyllene alcohol gives clovene (Bell and Henderson, *loc. cit.*), which is in agreement with formula (XXIV).

The results described in this, and in our previous paper on caryophyllene allow several aspects of the stereochemistry of the molecule to be clarified. We commence our discussion with the C_{12} dicarboxylic acid (VI). The smooth formation of the precursor (IX) of this acid could hardly be effected unless the *cyclo*butane ring were fused *cis* to the *cyclo*pentane ring. The C_{12} acid (VI) forms an anhydride with great ease merely on melting.

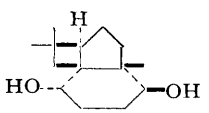

(XXV)

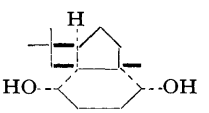

(XXVI)

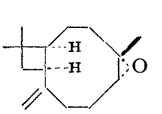

(XXVII)

This is the property of a *cis*- rather than of a trans-*cyclo*pentane-1 : 2-dicarboxylic acid (see Beilstein, " Handbuch der Organischen Chemie," 4th Edn., Vol. IX, p. 728). The stereochemistry of the C_{12} acid can, therefore, be formulated as in (XXV).

The tricyclic hydroxy-ketone $C_{14}H_{22}O_2$ must, therefore, have the stereochemistry indicated in either (XXVI) or (XXVII). The configuration of the carbon atom carrying the secondary hydroxyl group will depend upon whether the ring double bond in caryophyllene is *cis* [as in (III)] or *trans*. If the former is correct then (XXVII) represents the hydroxy-ketone, if the latter (XXVI). [We have assumed, of course, a *trans*-opening of the oxide ring in (VII) ⟶ (VIII) ⟶ (IX).] The available evidence indicates that the ring double bond in caryophyllene is *cis*. Thus, unlike *trans-cyclo*octene (which is the only available analogue in the absence of a *trans-cyclo*nonene) (see Ziegler and Wilms, *Annalen*, 1950, **567**, 1), caryophyllene and dihydrocaryophyllene are stable substances not polymerising readily. They do not react vigorously, if at all, with phenyl azide. A more subtle argument is the following (cf. Barton, *Experientia*, 1950, **6**, 316). If the six-membered ring in (XXVI) and (XXVII) adopts the more probable chair conformation, then the hydroxyl group of (XXVI) will be equatorial, but of (XXVII) polar. Reduction of the diketone (X) with sodium and alcohol should give the more stable diequatorial glycol (XXVIII; on the basis of the chair conformation), whereas similar reduction of the tricyclic hydroxy-ketone (IX) should give (XXVIII) or (XXIX) depending on whether (XXVI) or XXVII) is a correct representation of the stereochemistry. Experimentally *different* glycols were formed in the two reactions, and therefore the view that (XXVII) represents the stereochemistry of (IX) receives support.


(XXVIII)


(XXIX)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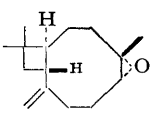

(XXXI)

These arguments lead to the conclusion that the stereochemistry of caryophyllene monoxide must be represented as in (XXX) or as in (XXXI). Although the evidence is not final it is more likely that the *cis*-fusion (XXX) of the *cyclo*butane ring is correct. This would explain better the ready formation of β-caryophyllene alcohol (XIII) and of the Treibs glycol (XIV), compounds in which the four-membered ring is fused to a seven-membered ring.

It will be clear from the results summarised above, and from earlier work in the caryophyllene field, that the electrophilic reagents OH^+ and H^+, as would be expected, attack preferentially the endocyclic double bond. In a recent communication (*Chem. and Ind.*, 1951, 464) Dawson, Ramage, and Wilson propose that the long-known caryophyllene nitrosite is formed by addition to the exocyclic methylene group. It is necessary to mention evidence which shows that this view is incorrect. First, caryophyllene nitrosite exhibits a strong band at 11·3 μ, indicative of an exocyclic methylene group. This band is also present in the spectrum of caryophyllene and of caryophyllene oxide. Secondly, Ramage and Simonsen (*J.*, 1935, 1581) showed that ozonolysis of caryophyllene nitrosite gave formaldehyde and a crystalline ketone $C_{14}H_{22}O_5N_2$. These facts cannot be explained by the hypothesis of Dawson, Ramage, and Wilson (*loc. cit.*) and we see no reason to

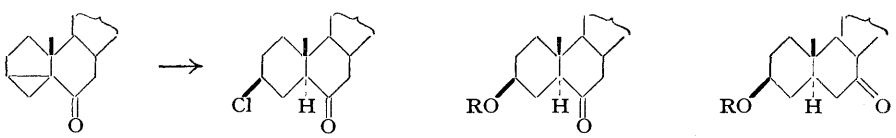
disregard the conclusion reached earlier by Ramage and Simonsen (*loc. cit.*) that the nitrosite retains the exocyclic methylene group. The interpretation of further experimental facts presented by Dawson, Ramage, and Wilson (*loc. cit.*) is, therefore, not valid.

The absorption spectra of ketonic 2 : 4-dinitrophenylhydrazones can often be used to obtain useful information with regard to the number of double bonds in conjugation with the keto-group (Braude and Jones, *J.*, 1945, 498; Roberts and Green, *J. Amer. Chem. Soc.*, 1946, **68**, 214; Djerassi and Ryan, *ibid.*, 1949, **71**, 1000). Whilst acetone 2 : 4-dinitrophenylhydrazone absorbs at 364 mμ (cf. Braude and Jones, *loc. cit.*) the maximum is displaced to 368 mμ for saturated steroidal 3-ketones of the *allo*cholane series (Djerassi and Ryan, *loc. cit.*). As has been mentioned above, the lower-melting isomer of the methyl ester (XVII; R = Me) 2 : 4-dinitrophenylhydrazone of the $C_{13}H_{20}O_3$ keto-acid showed an abnormally displaced maximum at 375 mμ. This displacement may be due to the conjugating power of the *cyclo*butane ring. The abnormal displacement of the band of the methyl *cyclo*propyl ketone derivative (see Table) (Roberts and Green, *loc. cit.*) with respect to that of the acetone derivative and of that of 3 : 5-*cyclo*cholestan-6-one (XXXII) 2 : 4-dinitrophenylhydrazone with respect to that of 6-keto- (XXXIII; R = Ac) and of 7-keto- (XXXIV; R = Ac)-cholestanyl acetate 2 : 4-dinitrophenylhydrazone would appear to support this view. However this explanation may require further qualification since the position of the maximum for the higher-melting isomer of the methyl ester 2 : 4-dinitrophenylhydrazone of the $C_{13}H_{20}O_3$ keto-acid was normal at 369 mμ. Other data of interest are also summarised in the Table.

2 : 4-Dinitrophenylhydrazone of	Abs. max. in $CHCl_3$ $\lambda_{max.}$, mμ	$\varepsilon_{max.}$	Ref.
$C_{14}H_{22}O_2$ tricyclic hydroxyketone (IX)	371	29,000	1
$C_{14}H_{20}O_2$ tricyclic diketone (X)			
mono-derivative	368	24,000	1
bis-derivative	369	44,000	2
$C_{13}H_{20}O_3$ keto-acid methyl ester			
lower-melting isomer	375	25,000	2
higher-melting isomer	369	22,500	2
6-Ketocholestan-3β-yl acetate	369	25,000	2
7-Ketocholestan-3β-yl acetate	370	25,000	2
3β-Chlorocholestan-6-one	367	23,000	2
3 : 5-*cyclo*Cholestan-6-one (*i*-cholestenone)	380	25,000	2
Methyl *cyclo*propyl ketone	371	22,500	2
*cyclo*Butyl methyl ketone	367	22,500	3
Acetone	364	23,500	2

1, Barton and Lindsey, *J.*, 1951, 2988; 2, Experimental, this paper; 3, first prepared by Mariella and Raube, *J. Amer. Chem. Soc.*, 1952, **74**, 518; see also Pinson and Friess, *ibid.*, 1950, **72**, 5333.

It was felt that the maximum for the 3 : 5-*cyclo*cholestan-6-one derivative at 380 mμ was so displaced owing to the conjugating power of the *cyclo*propane ring as to require confirmation of its structure. Treatment of the 2 : 4-dinitrophenylhydrazone with acetic–hydrochloric acids gave 3β-chlorocholestan-6-one (XXXV), characterised as the 2 : 4-

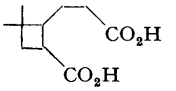
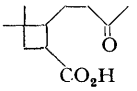


(XXXII) (XXXV) (XXXIII) (XXXIV)

dinitrophenylhydrazone. The latter compound was prepared from an authentic specimen of 3-chloro-ketone obtained in a known way from cholesteryl chloride. The formation of the 3β-chloro-compound confirms the constitution assigned.

After the completion of this manuscript there appeared an important paper by Dawson and Ramage (*J.*, 1951, 3382), recording the synthesis of homocaryophyllenic acid (XXXVI). Dawson and Ramage also report the degradation of the keto-acid $C_{11}H_{18}O_3$, an important ozonolysis fragment of caryophyllene (Semmler and Mayer, *Ber.*, 1911, **44**, 3657; for discussion see Barton and Lindsey, *loc. cit.*), to caryophyllenic acid by oxidation with potassium

permanganate. This is also significant as it proves that the keto-acid $C_{11}H_{18}O_3$ has formula (XXXVII). These results, taken in collaboration with our own work, account rigidly for every carbon atom in the caryophyllene molecule.

(XXXVI)  ←  (XXXVII)

Mainly on the basis of the infra-red spectrum Eschenmoser and Günthard (*Helv. Chim. Acta*, 1951, **34**, 2338) have independently proposed (XXIII) as a representation of clovene. This formula was also suggested to us independently in a private communication from Mr. A. W. Burgstahler (Harvard University).

Experimental

M. p.s are uncorrected. All rotations were measured in chloroform solution; the values recorded have been approximated to the nearest degree. Ultra-violet absorption spectra were determined in absolute ethanol solution (unless specified to the contrary) by use of a Unicam Spectrophotometer, Model SP 500. Infra-red measurements were kindly carried out in carbon disulphide solution by Mr. J. L. Hales on a modified Hilger double-beam spectrometer at the D.S.I.R. Chemical Research Laboratory, Teddington.

Light petroleum refers throughout to the fraction of b. p. 40—60°.

1 : 9-*Dihydroxy*-4 : 4 : 8-*trimethyltricyclo*[6 : 3 : 1 : $0^{2,5}$]*dodecane* (XIV); $C_{15}H_{26}O_2$ *Glycol.*—In agreement with Treibs (*Chem. Ber.*, 1947, **80**, 56) we had no difficulty in isolating the glycol $C_{15}H_{26}O_2$ from the residues remaining after the distillation of caryophyllene oxide. Purified by distillation and recrystallisation from light petroleum or, for larger amounts, from cold ether, it had m. p. 106—107°, $[\alpha]_D$ −5° (c = 2·00) (Found: C, 74·8; H, 10·8. Calc. for $C_{15}H_{26}O_2$: C, 75·55; H, 11·0%). The glycol was saturated to bromine, to tetranitromethane, and to potassium permanganate. It showed no absorption in the 195—220-mμ region. It was unaffected by treatment with chloroformic hydrogen chloride.

By reaction with excess of acetic anhydride in pyridine at room temperature overnight it furnished a *monoacetate* (XX) (*ca.* 100%). Recrystallised from light petroleum this had m. p. 104—105°, $[\alpha]_D$ +27° (c = 2·23) (Found: C, 72·3; H, 9·9. $C_{17}H_{28}O_3$ requires C, 72·8; H, 10·05%). There was a pronounced depression in m. p. on admixture with the original glycol. The monoacetate was unresponsive to tests for unsaturation.

1-*Hydroxy*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{2,5}$]*dodecan*-9-*one* (XV).—The $C_{15}H_{26}O_2$ glycol (see above) (500 mg.) in "AnalaR" acetic acid (10 ml.) was treated with chromium trioxide (170 mg.) in water (1 ml.) and "AnalaR" acetic acid (5 ml.) and left at 5° for 2 days. After being worked up in the usual way the *keto-alcohol* was recrystallised from chloroform–light petroleum and had m. p. 104°, $[\alpha]_D$ −74° (c = 2·49), $\lambda_{max.}$ 290—292 mμ, $\varepsilon_{max.}$ = 40 (Found: C, 76·65; H, 10·35. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). The keto-alcohol gave no colour with ferric chloride and was unresponsive to tests for unsaturation.

The keto-alcohol (250 mg.) with 94% hydrazine (2 ml.) and a solution of sodium (250 mg.) in absolute ethanol (6 ml.) was heated at 180° overnight. The reaction product, worked up in the usual way and recrystallised from light petroleum, gave 200 mg. of β-caryophyllene alcohol, $[\alpha]_D$ −3·5° (c = 1·98; 2-dm. tube), m. p. and mixed m. p. 93—94° with an authentic sample (see below) of the same m. p. and rotation.

1 : 10-*Dihydroxy*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 1 : $0^{2,5}$]*dodec*-10-*en*-9-*one* (XVI; R = H).—The keto-alcohol (XV) (400 mg.) was heated for 2 hours with selenium dioxide (200 mg.) in refluxing ethanol (10 ml.). The deposited selenium was removed and the filtrate diluted with water and extracted with ether. The ethereal extract was in turn extracted with 5% aqueous potassium hydroxide, and the alkaline solution acidified and re-extracted into ether. Drying (Na_2SO_4) and evaporation of the final extract gave the crystalline *dodecenone* (100 mg.). Recrystallised from benzene it had m. p. 141—142°, $[\alpha]_D$ +85° (c = 2·19), $\lambda_{max.}$ 276 mμ, $\varepsilon_{max.}$ = 6200 (Found: C, 71·3; H, 8·55. $C_{15}H_{22}O_3$ requires C, 71·95; H, 8·85%). It gave a transient purple colour with aqueous-ethanolic ferric chloride.

Excess of acetic anhydride in pyridine at room temperature overnight gave the *acetate*, m. p. 140—141° (from methanol), $[\alpha]_D$ +88° (c = 2·08), $\lambda_{max.}$ 245 mμ, $\varepsilon_{max.}$ = 5500 (Found: C, 69·7; H, 8·1. $C_{17}H_{24}O_4$ requires C, 69·85; H, 8·25%). There was a pronounced depression in m. p. on admixture with the parent diosphenol.

Derivatives of 2-*Keto*-4 : 8 : 8-*trimethyl*bicyclo[5 : 2 : 0]*nonane*-4-*carboxylic Acid* (XVII).—

(*a*) To the acetate (see above) (3·5 g.) in " AnalaR " acetone (25 ml.) were added at room temperature (occasional cooling), with shaking, 400 ml. of a solution of potassium permanganate (6·3 g., 3·33 atoms of oxygen) in the same solvent (600 ml.). The first 350 ml. were decolorised rapidly. The mixture was left at room temperature until the permanganate colour had disappeared (1 hour). A further 100 ml. of the solution was then added and then, after 7 hours (decolorisation) the final 100 ml. The mixture was left overnight, excess of permanganate removed by methanol, and the acetone solution decanted from the manganese dioxide and evaporated *in vacuo*. The residue was combined with the manganese dioxide, and dilute sulphuric acid and sodium sulphite were added until all the solid had passed into solution. The solution was extracted thoroughly with ether. The extracted products were separated into acid and neutral fractions with sodium hydrogen carbonate. The former was methylated and treated with 2 : 4-dinitrophenylhydrazine in the usual way, and the product chromatographed over alumina (Savory and Moore's Standardised). Elution with benzene gave three crystalline fractions, recrystallised from chloroform–methanol as beautiful square plates of the *methyl* ester 2 : 4-*dinitrophenylhydrazone*, m. p. 169—170°, $\lambda_{max.}$ 375 mμ, $\varepsilon_{max.}$ = 22,000 (in chloroform) (Found : C, 57·8; H, 6·0; N, 13·1. $C_{20}H_{26}O_6N_4$ requires C, 57·4; H, 6·25; N, 13·4%). Further elution with benzene gave a small quantity of the stereoisomeric methyl ester 2 : 4-dinitrophenylhydrazone, m. p. 184·5—185·5° [see (*c*) below].

(*b*) The diosphenol (250 mg.) in methanol (10 ml.) containing potassium hydroxide (300 mg.) was treated with perhydrol (1 ml.) added in small portions with shaking. After an hour at room temperature the mixture was worked up in the usual way and separated into acid (sodium hydrogen carbonate) and neutral fractions. The latter was negligible. The oily acid fraction with diazomethane gave an oily dimethyl ester, which showed no selective absorption in the ultra-violet; this was dehydrated with redistilled phosphorus oxychloride (1 ml.) in dry pyridine (10 ml.) overnight at room temperature. After working up in the usual way the dehydrated product was filtered through alumina in benzene solution. The eluate showed $\lambda_{max.}$ 224 mμ, $\varepsilon_{max.}$ = 3000, corresponding probably to about 25% of αβ-unsaturated ester. It showed no tendency to crystallise. The mixture of unsaturated esters in acetic acid (30 ml.) was ozonised at room temperature until the absorption band at 224 mμ had disappeared (15 minutes). The acetic acid solution was treated with zinc dust on the steam-bath for 30 minutes. After removal of the zinc by filtration the reaction product was extracted with ether after dilution with water, the ether removed, and the residue treated with 2 : 4-dinitrophenylhydrazine in the usual way. The resultant 2 : 4-dinitrophenylhydrazone was purified by chromatography over alumina as described in (*a*) above. Recrystallisation from chloroform–methanol gave the same methyl ester 2 : 4-dinitrophenylhydrazone, m. p. 169—170°, undepressed in m. p. with a specimen of the same m. p. prepared as above (Found : C, 57·2; H, 6·0; N, 12·9%).

(*c*) The hydroxy-dicarboxylic acid (500 mg.), prepared by oxidation of the diosphenol with alkaline hydrogen peroxide [see (*b*)], was refluxed with 50% (w/w) aqueous potassium hydroxide (10 g.) for 1 hour. The acidic reaction product was worked up in the usual way; it showed no high intensity selective absorption in the ultra-violet. It was methylated with diazomethane and treated with 2 : 4-dinitrophenylhydrazine as before. The mixture of 2 : 4-dinitrophenylhydrazones was chromatographed over alumina, elution being by benzene as in (*a*) above. The more easily eluted 2 : 4-dinitrophenylhydrazone formed in considerably greater amount was identical (m. p. and mixed m. p.) with that described in (*a*) and (*b*) above. The more difficultly eluted iso-*form* of the *methyl* ester 2 : 4-*dinitrophenylhydrazone* crystallised from chloroform–methanol in needles, m. p. 184·5—185·5°, $\lambda_{max.}$ 369 mμ, $\varepsilon_{max.}$ = 22,500 (in chloroform) (Found : C, 57·8; H, 6·5; N, 13·3. $C_{20}H_{26}O_6N_4$ requires C, 57·4; H, 6·25. N, 13·4%).

(*d*) Each of the methyl ester 2 : 4-dinitrophenylhydrazones described above (200 mg.) was heated under reflux with concentrated hydrochloric acid (2 ml.) in " AnalaR " acetic acid (10 ml.) for ½ hour. This procedure did *not* hydrolyse the ester grouping but largely removed the 2 : 4-dinitrophenylhydrazine residue. The reaction products were re-treated with 2 : 4-dinitrophenylhydrazine and then chromatographed as recorded in (*a*), (*b*), and (*c*) above. In both cases the same mixture of the two methyl ester 2 : 4-dinitrophenylhydrazones, m. p.s 169—170° and 184·5—185·5°, resulted. The identities were confirmed by mixed m. p.s. The isomer of m. p. 169—170° predominated over that of m. p. 184·5—185·5° (product ratio very approximately 10 : 1).

(*e*) The methyl ester 2 : 4-dinitrophenylhydrazone of m. p. 169—170° (300 mg.) was refluxed with potassium hydroxide (500 mg.) in methanol (10 ml.) for 3 hours. Working up in the usual way and separation into neutral and acid fractions gave only 50 mg. of the latter. It was concluded that the carbomethoxyl group is not readily hydrolysed.

β-*Caryophyllene Alcohol.*—Caryophyllene (see Part I) was hydrated according to Asahina and Tsukamoto (*Chem. Zentr.*, 1922, III, 826). β-Caryophyllene alcohol was thus obtained without difficulty. Recrystallised from light petroleum the pure alcohol had m. p. 93—94°, $[\alpha]_D$ −3° (c = 2·07; l = 2).

Clovene (XXIII) *and Its Derivatives.*—Clovene (2·5 g.), obtained by the Asahina and Tsukamoto hydration process (see above), in " AnalaR " acetic acid (40 ml.) was oxidised by chromium trioxide (3·5 g.) in water (2 ml.), diluted with more acetic acid (20 ml.), and left for 4 days at room temperature according to Ruzicka and Gibson's method (*loc. cit.*). In this way clovenic acid was obtained without difficulty. Recrystallised from ethanol it had m. p. 190—191° (decomp.), $[\alpha]_D$ +31° (c = 1·53 in absolute ethanol). Clovenic acid was also prepared by oxidation of clovene with concentrated nitric acid.

Clovenic acid (100 mg.) was heated with concentrated hydrochloric acid (2 ml.) at 180° for 6 hours. Working up in the usual way gave an oil (clovenic anhydride) which, on dissolution in potassium hydroxide solution and acidification, gave back clovenic acid unchanged (m. p. and mixed m. p.). In a similar experiment clovenic acid (200 mg.) was heated with acetic anhydride (2 ml.) at 220° for 6 hours. Working up as before gave back clovenic acid unchanged (m. p. and mixed m. p.).

1-*Chloro*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{2:5}$]*dodecane* (XIX) *and Its Derivatives.*—β-Caryophyllene alcohol (222 mg.) and phosphorus pentachloride (210 mg.) were gently warmed on the steam-bath until all was in solution. Working up in the usual way and recrystallisation from aqueous methanol afforded the chloride, m. p. 66—67°, $[\alpha]_D$ +6·5° (c = 3·77), in beautiful plates (yield, almost quantitative).

The monoacetate (XX) (266 mg.) and phosphorus pentachloride (220 mg.) were warmed gently on the steam-bath until reaction was complete. Working up in the usual way afforded 9-*acetoxy*-1-*chloro*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{2:5}$]*dodecane* (XXI), which from aqueous methanol formed beautiful needles, m. p. 125—126°, $[\alpha]_D$ +42° (c = 1·97) (Found: C, 68·8; H, 8·9; Cl, 11·85. $C_{17}H_{27}O_2Cl$ requires C, 68·3; H, 9·1; Cl, 11·85%). It gave a strongly positive Beilstein test.

This chloro-acetate (2 g.) was hydrolysed by refluxing 5% methanolic potassium hydroxide for 30 minutes. The product could not be crystallised, so it was oxidised in " AnalaR " acetic acid solution (50 ml.) with a slight excess of chromic acid, giving 1-*chloro*-4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{2:5}$]*dodecan*-9-*one* (XXII), m. p. 45—46° (from methanol), $[\alpha]_D$ −69° (c = 2·45) (Found: Cl, 14·6. $C_{15}H_{23}OCl$ requires, Cl, 13·9%). It gave a 2 : 4-*dinitrophenylhydrazone*, recrystallised from methanol after filtration in benzene solution through alumina and having m. p. 145—146°, $\lambda_{max.}$ 368 mμ $\varepsilon_{max.}$ = 23,000 (Found: N, 12·8. $C_{21}H_{27}O_4N_4Cl$ requires N, 12·9%).

The above chloro-ketone (2 g.) was heated with selenium dioxide (0·9 g.) in boiling ethanol (50 ml.) for 2 hours. After being worked up in the usual way the product was separated into acid (5% aqueous sodium hydroxide) and neutral fractions. The latter contained a high-melting organic selenium compound which was not investigated. The acid fraction was oxidised by alkaline hydrogen peroxide as for the diosphenol (see above), and the resultant acid fraction (extracted by sodium hydrogen carbonate from ether) was heated under reflux with 50% aqueous potassium hydroxide (25 ml.) for 1 hour. After the usual working up the acid fraction (extracted with sodium hydrogen carbonate) was esterified with diazomethane and then converted into the 2 : 4-dinitrophenylhydrazone. Chromatography over alumina in benzene solution gave the more stable $C_{13}H_{20}O_3$ keto-acid methyl ester 2 : 4-dinitrophenylhydrazone (identified by m. p. and mixed m. p.).

Bis-2 : 4-*dinitrophenylhydrazone of the Diketone* (X).—The tricyclic diketone (Barton and Lindsey, *J.*, 1951, 2988) was treated with 2 : 4-dinitrophenylhydrazine in methyl alcohol and hydrochloric acid under reflux for 30 minutes. Working up in the usual way and chromatography over alumina in benzene solution afforded the *bis*-2 : 4-*dinitrophenylhydrazone*. Recrystallised from ethyl acetate this had m. p. 260—261° (Found: N, 19·4. $C_{26}H_{28}O_8N_8$ requires N, 19·3%).

Reduction of the Tricyclic Ketone (X).—The tricyclic diketone (Barton and Lindsey, *loc. cit.*) (500 mg.) in *n*-propyl alcohol (25 ml.) was reduced under reflux by sodium until saturated. Working up in the usual way gave the required *glycol*, m. p. 181—182° (from chloroform), $[\alpha]_D$ −43° (c = 0·56) (Found: C, 74·3; H, 10·7. $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%).

Reduction of the Tricyclic Hydroxy-ketone (IX).—The hydroxy-ketone (Barton and Lindsey, *loc. cit.*) (500 mg.) was reduced as immediately above. Recrystallised from chloroform–light petroleum the derived glycol had m. p. 159—159·5°, $[\alpha]_D$ −69° (c = 1·24) (Found: C, 75·1;

H, 10·95. $C_{14}H_{24}O_2$ requires C, 74·95; H, 10·8%). There was a pronounced depression in m. p. on admixture with the isomeric glycol (see above) of m. p. 181—182°.

6- *and* 7-*Ketocholestan*-3β-*yl Acetate* 2 : 4-*Dinitrophenylhydrazone*.—6-Ketocholestan-3β-yl acetate (Barton and Cox, *J.*, 1948, 783) was converted into the 2 : 4-*dinitrophenylhydrazone* in the usual way. Purified by chromatography in benzene solution over alumina and recrystallisation from ethyl acetate–ethanol this had m. p. 172—173° (Found : N, 9·1. $C_{35}H_{52}O_6N_4$ requires N, 8·95%).

The 2 : 4-*dinitrophenylhydrazone* of the 7-ketone, prepared and purified as above and recrystallised from chloroform–methanol, had m. p. 185—186° (Found : N, 9·1%).

3 : 5-cyclo*Cholestan*-6-*one* 2 : 4-*Dinitrophenylhydrazone*.—3 : 5-*cyclo*Cholestan-6-one (*i*-cholestenone) was converted into the 2 : 4-*dinitrophenylhydrazone* in the usual way but at room temperature. Purified as above, and recrystallised from chloroform–methanol, it had m. p. 178—179° (Found : N, 10·0. $C_{33}H_{48}O_4N_4$ requires N, 9·9%).

This 2 : 4-dinitrophenylhydrazone (250 mg.) in " AnalaR " acetic acid (10 ml.) was refluxed with concentrated hydrochloric acid (1 ml.) for 2 hours. Working up in the usual way and chromatography over alumina (eluting with benzene) gave 3β-chlorocholestan-6-one which, recrystallised from methanol, had m. p. 130—131°. This was characterised by conversion into the 2 : 4-dinitrophenylhydrazone (see below).

3β-*Chlorocholestan*-6-*one* 2 : 4-*Dinitrophenylhydrazone*.—3β-Chlorocholestan-6-one, m. p. 129—130° (Windaus and Dalmer, *Ber.*, 1919, **52**, 162), gave a 2 : 4-*dinitrophenylhydrazone* which, when purified by chromatography in benzene over alumina and recrystallisation from chloroform–methanol, had m. p. 197—198° (Found : N, 9·35. $C_{33}H_{49}O_4N_4Cl$ requires N, 9·3%). It gave a strongly positive Beilstein test. There was no depression in m. p. on admixture with the 2 : 4-dinitrophenylhydrazone of the same m. p. obtained (see above) by the action of acetic–hydrochloric acid on 3 : 5-*cyclo*cholestan-6-one 2 : 4-dinitrophenylhydrazone.

Properties of 2 : 6 : 6-*Trimethyl*bicyclo[3 : 2 : 0]*heptane*-1 : 2-*dicarboxylic Acid* (VI).—The anhydride of this acid (see Barton and Lindsey, *loc. cit.*) was treated with bromine in purified thionyl chloride under reflux for 6 hours, with bromine in thionyl chloride at 115° (sealed tube) for 15 hours, and with bromine alone at 110° (sealed tube) for 15 hours. In each case starting material was recovered unchanged, characterised by hydration (boiling water) to the parent dicarboxylic acid (m. p. and mixed m. p.). More drastic conditions of attempted bromination led to intractable products. The dicarboxylic acid (750 mg.) was recovered unchanged after being heated at 180° in 20 ml. of concentrated hydrochloric acid for 5 hours. Heating overnight gave only intractable products. Similar experiments were carried out with the anhydride at 220° in acetic anhydride.

The dicarboxylic acid (400 mg.) was converted into its dimethyl ester with diazomethane. The ester was heated with 10% methanolic potassium hydroxide (50 ml.) for 4 hours. Unchanged neutral material (200 mg.) was recovered. The experiment was repeated with 50% methanolic potassium hydroxide for 6 hours : in this case there was no unchanged neutral fraction. It is to be concluded that both the carboxyl groups in the dicarboxylic acid are sterically hindered.

Treatment of Caryophyllene and of Dihydrocaryophyllene with Phenyl Azide.—Caryophyllene, $[\alpha]_D$ −9·13° (homogeneous) (500 mg.), was treated with phenyl azide (750 mg.). Admixture led to no spontaneous reaction or evolution of heat. After 6 months at room temperature there was still no indication of reaction. The same results were obtained with dihydrocaryophyllene, b. p. 110°/4 mm., n_D^{20} 1·4888, $[\alpha]_D^{20}$ −23·15° (homogeneous); working up gave unchanged dihydrocaryophyllene.

We thank the Government Grants Committee of the Royal Society, the Central Research Fund of London University, and Imperial Chemical Industries Limited for financial assistance. We are indebted to Sir John Simonsen, F.R.S., for his interest in, and encouragement of, this work. The clove-bud sesquiterpenes used for the extraction of caryophyllene were generously provided by Mr. Dewhurst of White, Tompkins, and Courage Ltd., Reigate, Surrey. This work was carried out by one of us (T. B.) whilst in receipt of a Research Fellowship from the Norges Teknisk-Naturvitenskapelige Forskningsråd. Professor J. D. Roberts of the Massachusetts Institute of Technology, Boston, kindly supplied the specimen of methyl *cyclo*propyl ketone 2 : 4-dinitrophenylhydrazone. A generous specimen of *cyclo*butyl methyl ketone was kindly provided by Drs. S. L. Friess and R. Pinson.

Birkbeck College, London, W.C.1. [*Received, January 17th*, 1952.]