*Clovene and β-Caryophyllene Alcohol.**

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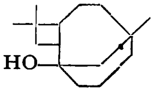
Evidence is advanced to show that clovene, as ordinarily obtained, is a mixture of isomeric sesquiterpenes inseparable by distillation. Bromination of ordinary clovene yields a mixture of two stable isomeric dibromides which, upon fractional crystallisation, have yielded the first solid derivatives of this oily terpene. The oxidation of pure clovene furnishes clovenic acid in high yield, and additional evidence has been secured proving that clovene lacks hydrogen atoms alpha to the double bond.

The reduction of clovenic acid furnishes a glycol that is extremely resistant to reagents that usually effect the *neo*pentyl rearrangement. Dehydration with potassium hydrogen sulphate gives, as the main product, a cyclic ether that is adamantine to ring fission and on oxidation furnishes a very stable lactone.

The carbon skeleton of pure clovene has been shown unequivocally to be identical with that of a tricyclic glycol, the structure of the latter being established by Barton and his co-workers.

Whilst β-caryophyllene alcohol would be expected to yield clovene on dehydration with Wagner–Meerwein rearrangement, and is so reported in the literature, this is shown conclusively not to be the case. Instead, a new structural isomer of clovene is obtained, termed *pseudo*clovene.

The tricyclic monounsaturated sesquiterpene, clovene, is reported to be formed from the dicyclic β-caryophyllene by a variety of methods. Using the Bertram–Walbaum reagent (glacial acetic and dilute sulphuric acids) Wallach and Walker (*Annalen*, 1892, **271**, 285) obtained the oily hydrocarbon (clovene) together with a solid tricyclic alcohol, $C_{15}H_{26}O$, β-caryophyllene alcohol. This extremely stable alcohol, boiling at 287—289° without decomposition, readily furnished the chloride, bromide, and iodide on treatment with the appropriate phosphorus halide, and from the chloride the corresponding acetate was obtained (Henderson, McCrone, and Robertson, *J.*, 1929, 1368). Because of its extreme resistance towards oxidising agents the alcohol was assumed to be tertiary in nature, with the hydroxyl group probably located on a bridge-head carbon atom. This assumption was supported by the observation that under very vigorous oxidising conditions the substance was drastically degraded to a liquid acid, $C_{10}H_{12}O_3$ (Bell and Henderson, *J.*, 1930, 1971). In addition, Wallach and Walker (*loc. cit.*), by dehydration of β-carypohyllene alcohol with phosphoric oxide, obtained a hydrocarbon, $C_{15}H_{24}$, b. p. 261—263°, n_D^{18} 1·50066, which they assumed to be clovene because of its similarity to the isomerisation product of β-caryophyllene. The fact that clovene, in their hands, failed to be capable of regenerating β-caryophyllene alcohol lent support to the assumption of a bridge-head hydroxyl group, and suggested that dehydration was only effected with concomitant structural rearrangement.


(I)

The recent *X*-ray crystallographic determination of β-caryophyllene aclohol chloride (Robertson and Todd, *Chem. and Ind.*, 1953, 437) not only confirmed the original deductions concerning the bridge-head structure of the alcohol, but established the structure (I) and stereochemistry of the molecule as well.

By a modification of the above dehydration process Henderson, McCrone, and Robertson (*loc. cit.*) obtained a mixture of sesquiterpenes which were separated into (1) a compound thought to be clovene, b. p. 111—113°/10 mm., n_D^{20} 1·4980, and (2) another oil, termed *iso*clovene, b. p. 130—131°/12 mm., α_D^{14} −56·6°.

Dehydrohalogenation of caryophyllene dihydrochloride by quinoline or pyridine (Semmler and Mayer, *Ber.*, 1910, **43**, 3451) afforded a tricyclic sesquiterpene, b. p. 122—123°/13 mm., n_D^{20} 1·50246, α_D^{20} −57°, which it has been suggested is identical with clovene (Henderson, McCrone, and Robertson, *loc. cit.*; Simonsen and Barton, " The Terpenes," Cambridge Univ. Press, 1952, Vol. III, p. 66). A liquid monohydrochloride of caryo-

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* Much of the material presented in this paper has been described previously in abbreviated form (*Chem and Ind.*, 1953, 278, 749).

phyllene gave, on treatment with silver acetate in acetic acid, an oil, b. p. 118—124°/10 mm., n_D^{20} 1·4992, also considered to be clovene (Bell and Henderson, *loc. cit.*), together with the acetate of a tricyclic alcohol which when hydrolysed and dehydrated furnished an olefin, n_D^{17} 1·5004, likewise considered to be clovene.

The work of Asahina and Tsukamoto (*J. Pharm. Soc. Japan*, 1922, 463) showed that hydration of caryophyllene with Aschan's reagent (sulphuric acid monohydrate in ether) furnished, not only a mixture of clovene and β-caryophyllene alcohol, but also α-caryophyllene alcohol, m. p. 117°. The last, on dehydration with phosphoric anhydride (Bell and Henderson, *loc. cit.*) yielded clovene, b. p. 118—123°/12 mm., n_D^{17} 1·5000.

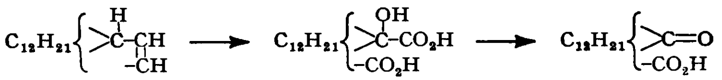
It is apparent, from the variations in the physical constants reported, that clovene has never been adequately characterised and that, owing to the lack of solid derivatives, no satisfactory criterion for either the purity or the identity of the terpene is available except its degradation to the dicyclic dibasic clovenic acid (Ruzicka and Gibson, *Helv. Chim. Acta*, 1931, **14**, 575). This acid, while of use for identification, cannot be used for the regeneration of pure clovene. It should also be pointed out that the yields of clovenic acid reported in the older literature have not exceeded 40%.

In our work with clovene it was considered essential to obtain pure material. Commercial caryophyllene from two sources was freed from traces of phenolic impurities by treatment with alkali. Hydration with Aschan's reagent furnished the expected β-caryophyllene alcohol and crude clovene, together with very low yields of α-caryophyllene alcohol, and a new hydration product, $C_{15}H_{26}O$, m. p. 70—71°. In most of our work, isolation was accomplished by using superheated steam (about 160°), and under these conditions no α-caryophyllene alcohol was obtained. It seems justified to conclude, therefore, that at the higher isolation temperature α-caryophyllene alcohol is completely dehydrated to clovene.

Fractional distillation of this crude clovene through an efficient column gave fractions boiling from 114·5° to 128·5° at 12·0 mm., with $\alpha_D^{25\cdot0}$ varying from $-20\cdot24°$ to $-54\cdot21°$. An infra-red absorption spectrum of an intermediate fraction proved identical with one later reported by Eschenmoser and Günthard (*Helv. Chim. Acta*, 1951, **34**, 2338) for their clovene purified by distillation.

Bromination of clovene (purified by distillation) gave, in relatively poor yield, a solid mixture of isomeric dibromides that was distillable *in vacuo* (b. p. 153—162°/1·0 mm.) with only slight decomposition. Fractional crystallisation from ethanol furnished the major isomeride, m. p. 71·0—71·5°, and the minor isomeride, m. p. 41—43°. These appeared be the first crystalline derivatives to have been prepared from clovene, and very pure specimens of clovene (b. p. 115·0°/12·5 mm., $n_D^{25\cdot0}$ 1·4913, $\alpha_D^{25\cdot0}$ $-23\cdot37°$) were regenerated from each dibromide by extended treatment with zinc dust. It is of significance that the bromine atoms in these isomerides are extremely inert. Thus, treatment of either dibromide with refluxing alcoholic potassium·hydroxide for 3 hours was without effect, and in boiling ethanol solution the action of zinc dust was only slight after 3 hours. Also of significance is that our very pure clovene furnished, on oxidation, clovenic acid in high yield. In this connection we also satisfied ourselves that the formation of clovenic acid proceeded without skeletal rearrangement (cf. Byers and Hickinbottom, *J.*, 1948, 1334), for the crystalline acid was formed by oxidation with chromic acid, alkaline permanganate (very slowly), or by the action of ozone followed by hydrogenation and then oxidation.

It was observed in our work with clovene purified only by distillation, that oxidation by several reagents gave clovenic acid together with two acidic by-products. One of these, after purification through its methyl ester, had the empirical formula $C_{14}H_{22}O_3$ and proved to be a monocarboxylic keto-acid. On the other hand, our very pure clovene gave none of this by-product, indicating that clovene, as ordinarily obtained, contains as an impurity an isomeric hydrocarbon possessing the partial structure :



$$C_{12}H_{21}\left\{\begin{array}{l}>\overset{H}{C}-\underset{\|}{C}H \\ \quad -CH\end{array}\right. \longrightarrow C_{12}H_{21}\left\{\begin{array}{l}>\overset{OH}{C}-CO_2H \\ -CO_2H\end{array}\right. \longrightarrow C_{12}H_{21}\left\{\begin{array}{l}>C=O \\ -CO_2H\end{array}\right.$$

and that the course of its oxidation is as suggested in the above sequence. All efforts to obtain a crystalline derivative of the keto-acid were without success.

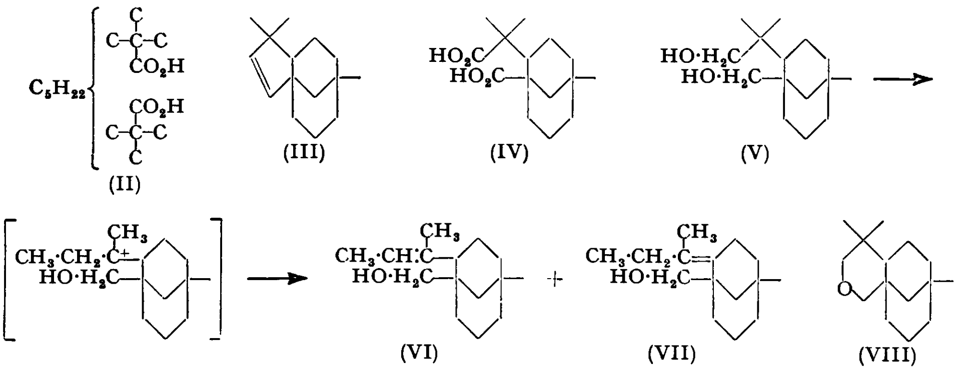
The second acidic by-product, obtained only in small quantities, had m. p. 101—102° and the formula $C_{12}H_{20}O_3$. It is presumed that this acid is also derived from the impurity in clovene. The acid was unstable, giving neutralisation equivalents that varied according to the method of determination. Paucity of material prevented further experimentation.

The neutral fraction, obtained from the oxidation of ordinary clovene with chromic anhydride, amounted to about 24% (by weight), and was investigated briefly. It contained mainly unchanged clovene, together with a high-boiling ketone, analysis of whose 2 : 4-dinitrophenylhydrazone showed it to be an unsaturated tricyclic monoketone, $C_{15}H_{22}O$.

In the Wohl–Ziegler reaction, ordinary clovene reacted very sluggishly and incompletely with *N*-bromosuccinimide. Isolation, *via* short-path distillation, furnished a dark yellow product, unstable unless kept under nitrogen at solid carbon dioxide temperature. This material gave very low analyses for bromine, and it was concluded that clovene probably contained no hydrogen atoms alpha to the double bond, and our attention turned to clovenic acid as a starting point for degradative work.

The failure of clovenic acid to give the diagnostic test characteristic of tertiary acids (Bistrzycki and Mauron, *Ber.*, 1907, **40**, 4370), owing to preferential anhydride formation, while not conclusive, was strongly indicative of the presence of two tertiary acid groupings, and this was confirmed as follows. Attempts to prepare the di-acid chloride by interaction with oxalyl chloride (Adams and Ulrich, *J. Amer. Chem. Soc.*, 1920, **42**, 599), a process that normally is successful with either dicarboxylic acids or their anhydrides, gave only clovenic anhydride. Attempted ammonolysis with gaseous ammonia on dimethyl clovenate in alcohol for 18 days resulted in only unchanged ester. Application of the Schmidt reaction (" Organic Reactions," John Wiley and Sons, New York, 1st Edn., p. 307), using the modification wherein clovenic acid and hydrazoic acid in benzene were treated with sulphuric acid dropwise (cf. Blair, *J.*, 1935, 1297), yielded only clovenic anhydride. The above experiments, when considered in conjunction with the stability of the acid towards nitric acid and other oxidising agents (Blair, *loc. cit.*) and towards isomerising conditions (Barton, Bruun, and Lindsey, *J.*, 1952, 2210), together with the facts that the acid resists bromination and ketonisation (Ruzicka and Gibson, *loc. cit.*), can only be accommodated by a di*neo*pentyl system, as in (II).

Reduction of clovenic acid to the corresponding glycol (V) should thus furnish a structure containing two *neo*pentyl groupings. In view of the work by the Whitmore school (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1932, **54**, 22, 3274, 3431, 3435, 4011; 1933, **55**, 1119, 3721, 4161; cf. Ingold, *J.*, 1923, **123**, 1706) on rearrangements in the *neo*pentyl system, it seemed reasonable to expect that an analogous rearrangement by the glycol, with concomitant dehydration, should give unsaturated products of predictable structures, amenable to degradation. Thus, if expression (III) is adopted for clovene (Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1951, 1910; *J.*, *loc. cit.*; Eschenmoser and Günthard, *loc. cit.*), reduction of



(II) (III) (IV) (V)

(VI) (VII) (VIII)

clovenic acid (IV), should yield the glycol (V), which on dehydration would be expected to furnish a mixture of olefins (VI and VII). It may be noted that the second carbinol grouping, since located on the bridge-head, would not be expected to be involved in the dehydration with rearrangement, since the requisite ring expansion from C_6 to C_7 would locate the positive charge at the bridge-head, and stabilisation *via* proton expulsion would result in formation of an ethylenic bond at the bridge-head of a system wherein *S* is less than ten (cf. Fawcett, *Chem. Reviews*, 1950, **47**, 219).

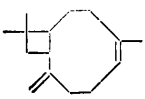
Lithium aluminium hydride reduction of either dimethyl clovenate or clovenic acid resulted in the smooth formation of a gummy, hygroscopic, immobile oil that was characterised through its crystalline diphthalate. On dehydration with fused potassium hydrogen sulphate one molecule of water was lost, with formation in good yield of a substance of m. p. 12·5°. Quantitative hydrogenation and acetylation, and semiquantitative bromination studies, proved this to contain about 10% of unsaturated alcohol, the rest being inert ethereal material that showed in the infra-red a strong absorption at 9·0 μ (1111 cm.$^{-1}$) (ether absorption). It is thus apparent that dehydration mainly proceeded to form the cyclic ether (VIII) (compare the ready dehydration of clovenic acid), there being very little of the hoped-for dehydration with rearrangement.

Oxidation of the above mixture of dehydration products with potassium permanganate in pyridine furnished a degraded keto-dicarboxylic acid, $C_{13}H_{20}O_5$, m. p. 178·5—180° (depressed to 149—150° on admixture with clovenic acid), in low yield, together with the main product, a neutral material, m. p. 93·0—94·5°, $C_{15}H_{24}O_2$. The latter was completely inert to basic hydrolysis, bromination, and oxidation, and showed no carbonyl reactions, behaviour reminiscent of that of the presumed lactone obtained by treatment of clovenic anhydride with phenylmagnesium bromide (Blair, *loc. cit.*). The lactonic structure of our product was confirmed by a strong absorption band at 5·88 μ (1700 cm.$^{-1}$) in the infra-red (oil paste).

Whilst analogy for lactone formation from a cyclic ether is found in the catalysed air-oxidation of tetrahydrofuran and tetrahydropyran to γ-butyrolactone and δ-valerolactone, respectively (Bremmer and Jones, B.P. 608,539, 1948), the extreme stability of our product must be due to steric reasons. The compound was completely stable to excess of refluxing hydrobromic–sulphuric acid for 30 hours, and was unaffected by chromic anhydride. It is of interest that the same keto-dicarboxylic acid, which is obviously derived from the unsaturated alcohol, and the lactone were obtained by treatment of the dehydration mixture with ozone, followed by chromic acid.

It unfortunately proved impossible to establish dehydration conditions that would furnish workable yields of rearranged dehydration products. Thus, concentrated sulphuric–toluene-*p*-sulphonic acid mixture gave, as the major product, a low-boiling material, $C_{15}H_{26}O$; this was a mixture of saturated and unsaturated components differing from those produced by potassium hydrogen sulphate, for on oxidation with potassium permanganate a very low yield of a diketo-dibasic acid, $C_{15}H_{24}O_6$, was obtained, together with a large neutral fraction that gave negative carbonyl and glycol tests. Oxidation of the mixture with chromic acid yielded a trace of a dibasic keto-acid, $C_{14}H_{22}O_5$, and a quantity of neutral material shown to be starting product mixed with a small amount of higher-boiling ketonic substance. With formic acid, a mobile oil (22%), $C_{15}H_{26}O$, was formed, the major (78%) fraction being the monoformate ester of clovene glycol. Oxidation of the minor component with potassium permanganate in pyridine formed a neutral product, saturated to bromine, that failed to respond to carbonyl reagents. A trace of solid acid, $C_{15}H_{24}O_6$, was also obtained, thought to be the diketo-dibasic acid mentioned above although mixed melting point determinations were inconclusive. The action of phosphoric oxide seemed initially more promising, for a mixture of saturated and unsaturated products was obtained, the latter containing material shown to be doubly unsaturated. Unfortunately, attempts to isolate the small amounts of these products in pure state by fractional distillation, or chromatography, or through formation of solid derivatives, were unsuccessful.

Evidence for the Structure of Clovene, and the Dehydration of β-*Caryophyllene Alcohol.*—Earlier work in these laboratories by Mr. Norman W. Atwater had shown that β-caryophyllene (IX) was cyclised by performic acid to a tricyclic glycol, both of whose hydroxyl groups were secondary since on oxidation a diketone was formed, characterised through its bis-2 : 4-dinitrophenylhydrazone. The same glycol (direct comparison through the courtesy of Professor D. H. R. Barton) had been prepared independently (Barton, personal communication; Aebi, Barton, and Lindsey, *Chem. and Ind.*, 1953, 748) by mild acid hydrolysis of β-caroyphyllene oxide (X). These authors established the probable structure of the glycol as (XI) originating *via* a logical mechanistic route from the oxide, and the diketone as (XII), with the supporting evidence of infra-red absorption data for five- and six-ring ketones. Finally, in an elegant series of reactions, they transformed the diketone (XII), into clovenic acid (IV). The relation of the carbon skeleton of the glycol, and its derived diketone, to that postulated for clovene (III) is obvious. We have therefore transformed both the diketone (XII) and clovene into a common structure, clovane, by quantitatively hydrogenating clovene and, in 76% yield, by Wolff–Kishner reduction of the diketone (XII).*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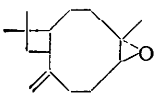
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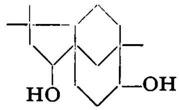

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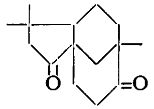

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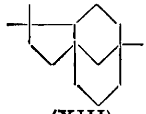
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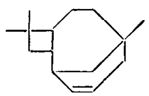
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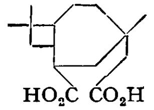

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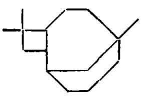
(XVI)

The above transformations, when considered in conjunction with the ultimate degradation of the glycol (XI) to clovenic acid (Aebi, Barton, and Lindsey, *loc. cit.*) unequivocally establishes the same carbon skeleton in clovene as in the glycol, and the structure of the latter cannot reasonably be doubted. If structure (III) is accepted for clovene, a direct relation should exist between clovene and β-caryophyllene alcohol (I), since dehydration with Wagner–Meerwein rearrangement of the latter would be expected to furnish the hydrocarbon. Indeed, the literature contains statements in support of this dehydration (Wallach and Walker; Henderson, McCrone, and Robertson, *locc. cit.*). Careful repetition of this dehydration (phosphoric oxide) has shown, however, that while the product closely resembles clovene in so far as its boiling point and refractive index are concerned, its rotation is of opposite sign, its infra-red absorption spectrum shows distinct differences, and its chemical behaviour is completely different. Thus, in contradistinction to clovene, the new dehydration product, which we have termed *pseudo*clovene, forms an unstable compound with bromine and on oxidation forms an oily dibasic acid isomeric with clovenic acid. Although clovenic acid is ditertiary, *pseudo*clovenic acid must contain α-hydrogen atoms, for it undergoes ready substitution in the Hell–Volhard–Zelinski reaction, forming a dibromo-acid that was characterised through its dimethyl ester. Further, *pseudo*clovene must contain hydrogen atoms alpha to the double bond, for, unlike clovene, it reacted smoothly with *N*-bromosuccinimide to form an unstable bromo-derivative.

Clovene and *pseudo*clovene must therefore be structural isomers. The number of dehydration products (without rearrangement) resulting from (I) is strictly limited, and on the basis of the evidence at hand, formula (XIV) is tentatively proposed for *pseudo*clovene, and (XV) for *pseudo*clovenic acid.

The question naturally arises of the rôle of β-caryophyllene alcohol in the formation of clovene from β-caryophyllene. The alcohol was recovered unchanged when treated with Aschan's reagent under the conditions used in the preparation of clovene, or with boiling 20% sulphuric acid for 4½ hours. However use of much more vigorous conditions than obtain for the hydration of β-caryophyllene, *i.e.*, in ether–concentrated sulphuric acid at 75° for 1 hour, gave a mixture of an unsaturated hydrocarbon (25%), not clovene, and a saturated hydrocarbon (75%). The formation of the latter is reminiscent of Oddo and

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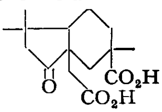
* During the oxidation of the glycol to the diketone a small amount of acidic material was obtained as a by-product, apparently the annexed keto-dicarboxylic acid; it results from oxidation of the diketone (cf. Aebi, Barton and Lindsey, *loc. cit.*).



Scandola's reduction (*Gazzetta*, 1909, II, **39**, 44) of several alcohols to alkanes by sulphuric acid. In our case ether–sulphuric acid was used, and preliminary cleavage of the ether to ethanol would furnish a readily oxidisable component. The structure of our saturated hydrocarbon must be (XVI), for oxidation of the hydrocarbon mixture with chromic acid resulted in the formation of β-caryophyllene alcohol, together with a small amount of a keto-acid, $C_{13}H_{22}O_3$, that formed an oily 2 : 4-dinitrophenylhydrazone and gave a methyl ester that did not undergo the haloform reaction. The formation of β-caryophyllene alcohol in this reaction was shown to be due to oxidation and not to hydration of a double bond (which would have to be located at the bridge-head), since the same reaction conditions, but without the oxidant, failed to yield the alcohol.

It thus is established that despite the logical structural relation between β-caryophyllene alcohol and clovene, it is not possible to effect the transformation in the laboratory. From this it must be concluded that the hydration of β-caryophyllene with Aschan's reagent takes at least two paths : in one the relatively stable β-caryophyllene alcohol is formed; in the other, clovene and other products are produced. It also seems certain that these two paths are mutually exclusive and presumably involve different ionic intermediates.

EXPERIMENTAL

Some of the analyses are by Mr. J. Walter, The John Hopkins University.

Clovene.—As a result of many comparative experiments, the procedure of Asahina and Tsukamoto (*loc. cit.*) was modified as follows. Concentrated sulphuric acid (900 g.) was added dropwise to ether (1700 ml.) in a 12-l. flask at 0°. To this solution was added 3 kg. of commercial caryophyllene (Dodge and Olcott, New York; previously extracted with dilute aqueous sodium hydroxide) at such a rate that the temperature remained below 10°. The mixture was kept overnight and then neutralised by the slow addition of technical sodium hydroxide flakes (600 g.) in 20% aqueous solution, after which solid sodium hydroxide (600 g.) was added carefully. Water was added occasionally, so that the final volume was about 9 l. The use of sodium hydroxide eliminated the excessive frothing that occurs if the recommended sodium carbonate is used. The final mixture, in two portions, was exhaustively distilled in steam pre-heated to 160°. The distillate was separated crudely into 1082 g. of solid and 1477 g. of oil. Recrystallisation of the solid from acetone gave pure β-caryophyllene alcohol, micro-m. p. 96·5—97° (Kofler hot stage).

Re-acidification of the distillation residue followed by exhaustive steam-distillation failed to furnish additional products. However, when steam-distillation at 100° was used, besides β-caryophyllene alcohol and clovene, a small amount of α-caryophyllene alcohol was obtained, having m. p. 118—119° (from acetone), together with a small amount of new hydration *product*, m. p. 70—71° (from acetone), isomeric with the caryophyllene alcohols (Found : C, 81·1; H, 11·7. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%).

Clovene from Florasynth Laboratories gave similar results.

Purification of Clovene by Distillation.—Crude clovene (1 l.) was combined with benzene (300 ml.) and dried by distillation of the benzene–water azeotrope at atmospheric pressure. The residue was then distilled under nitrogen through a 48-in. adiabatically jacketed Stedman column equipped with conical-type packing. At 12·0 mm., and with the column operating continuously for 24 hr., nine fractions were taken whose constants varied between the limits, b. p. 114·5—128·5°, $\alpha_D^{25\cdot0}$ −20·24° to −54·21°, $n_D^{25\cdot0}$ 1·4908—1·5032. Fractions 1—7 were combined (558·5 g.) and redistilled through the Stedman column, with arbitrary 25-ml. fractions, giving the tabulated fractions :

Fraction	B. p./12 mm.	$\alpha_D^{25\cdot0}$	$n_D^{25\cdot0}$
1	114·5—114·8°	−19·50°	1·4895
2—9	114·9—116·0	−20·21 to −21·20	1·4094—1·4912
10—12	116·0—116·0	−21·60 to −22·54	1·4925—1·4925
13—23	116·0—118·5	−22·85 to −38·17	1·4924—1·4910
24—25	119·3—120·5	−47·06 to −50·28	1·4901—1·4895

An infra-red absorption spectrum of fraction 6, b. p. 115·4°/12·0 mm., $\alpha_D^{25\cdot0}$ −20·80°, $n_D^{25\cdot0}$ 1·4909, was identical with that reported by Eschenmoser and Günthard (*loc. cit.*) for their pure clovene.

Purification of Clovene through the Dibromide.—Distilled clovene (30 g.) in carbon tetrachloride (200 ml.) was chilled to 0° and bromine (24 g.) in carbon tetrachloride (100 ml.) was added dropwise and with stirring during 12 hr. (temperature kept at 0°). The light yellow solution was allowed to warm to room temperature, was stirred for an additional 6 hr., washed with 5% bicarbonate solution and then water to neutrality, dried (Na_2SO_4), and evaporated *in vacuo*. The residue (32 g.) crystallised spontaneously. Fractional crystallisation from 95% ethanol gave a *dibromide* (38% of the crude product), m. p. 71·0—71·5° (Found: C, 49·65; H, 6·7. $C_{15}H_{24}Br_2$ requires C, 49·45; H, 6·65%), and an *isomer* (23%), m. p. 41—43° (Found: C, 49·4; H, 6·6%). Gravimetric bromine analyses were unsuccessful, since the compounds were not attacked by boiling alcoholic potassium hydroxide. The residue from the above crystallisation had m. p. 44—65°, and was not further separated.

Regeneration of Clovene.—The high-melting dibromide (21·0 g.) in 95% ethanol (300 ml.) was refluxed with zinc dust (8·7 g.) for 8 hr. The mixture was then poured into water and extracted with ether four times. The troublesome emulsion that formed was dispelled by making the aqueous layer slightly acidic. The extracts were washed with water until free from halide ion and dried (Na_2SO_4). After evaporation, the residual oil was fractionated through a short column and gave one fraction of colourless oil, b. p. 115·0°/12·5 mm., $n_D^{25\cdot0}$ 1·4913, $\alpha_D^{25\cdot0}$ −23·37°. The yield was 9·07 g. (77%) of pure *clovene* (Found: C, 88·3; H, 12·0. $C_{15}H_{24}$ requires C, 88·2; H, 11·8%).

Similar treatment of the low-melting dibromide gave clovene, b. p. 111—112°/11·5 mm., $n_D^{25\cdot0}$ 1·4902, $[\alpha]_D^{27\cdot0}$ −27·1° (in $CHCl_3$; *c* 3·13).

The Wohl–Ziegler Reaction.—Clovene, purified only by distillation (40 g.), was dissolved in carbon tetrachloride (200 ml.), and *N*-bromosuccinimide (35 g., 1 equiv.) was added. The mixture was refluxed for 16 hr. under infra-red radiation, at which point the reaction was complete. A portion of the product was distilled from a Hickman short-path still at 10^{-3} mm., to give two fractions. The first contained only 3·5% of bromine. The second (bath-temp. 50°) contained 10·7% (Calc. for $C_{15}H_{23}Br$: Br, 28·2%). Unless stored under nitrogen at −80°, the product decomposed. Unsuccessful attempts were made to free the bromide from contaminants *via* the β-naphthyl ether and the *S*-alkyl*iso*thiourea picrate.

Oxidations of Clovene.—(1) Ordinary clovene in carbon tetrachloride was oxidised with potassium permanganate while a stream of carbon dioxide was conducted through the mixture. After the usual working up, a 7·2% yield of pure clovenic acid was obtained together with 79·5% of neutral (starting) material.

(2) Treatment of ordinary clovene in ethyl acetate solution with ozone for 10 hr. at 0° was followed by reduction of the ozonide with hydrogen and 2% palladised calcium carbonate (49·6% of theoretical H_2 uptake). The thick residual oil was then oxidised with permanganate, yielding clovenic acid in 47% yield.

(3) Ordinary clovene was ozonised in methylene chloride (cf. Henne and Hill, *J. Amer. Chem. Soc.*, 1943, **65**, 752), then oxidised with hydrogen peroxide and finally permanganate. Clovenic acid was obtained in 41% yield.

(4) With chromium trioxide (Ruzicka and Gibson, *loc. cit.*) ordinary clovene formed clovenic acid in 51·5% yield.

(5) With clovene purified through the dibromide, chromium trioxide oxidation furnished the acid in 75% yield, the residue being unchanged hydrocarbon.

$C_{14}H_{22}O_3$ *Keto-acid.*—The acidic product (64 g.) obtained from the chromium trioxide oxidation of ordinary clovene was triturated in two portions (200 ml.) of acetone, to give 36 g. of white insoluble clovenic acid, m. p. 166—170°. Concentration of the acetone solution furnished an additional 3·2 g. of clovenic acid, and complete removal of the solvent left 25 g. of oily acid (61 parts of clovenic acid to 39 of oily keto-acid). The oily acid (25 g.) was refluxed for 24 hr. with methanol (25 ml.) and mixed alkanesulphonic acids (3 ml.) in chloroform (270 ml.), with anhydrous magnesium sulphate (Soxhlet) to remove the water formed. This gave 26·6 g. (96·4%) of crude ester that was fractionated through a 32 cm. Vigreux column and yielded the pure *methyl ester*, b. p. 123·5°, $n_D^{25\cdot0}$ 1·4800 (Found: C, 71·5; H, 9·5%; sap. equiv., 252·9. $C_{15}H_{24}O_3$ requires C, 71·4; H, 9·6%; sap. equiv., 252·4). Both the keto-acid and its methyl ester with 2 : 4-dinitrophenylhydrazine reagent readily formed yellow oils that darkened on storage. The oils could not be induced to crystallise, even after chromatographic purification. A variety of derivatives was tried unsuccessfully including the semioxamazide, *p*-phenylphenacyl ester, benzylamine salt, benzylamide, *p*-bromoanilide, and anilide.

On one occasion the crude, oily, acidic portion (from the acetone mull) was kept for several days dissolved in a minimum amount of light petroleum, while 2—3 g. of solid separated. The *substance* was very soluble in the usual organic solvents, but furnished white glistening needles [from ethanol–water (6 : 4)], m. p. 101—102° (Found: C, 68·3; H, 9·3. $C_{12}H_{20}O_3$ requires

C, 67·9; H, 9·5%); the neutralisation equivalent was: (1) dissolved in base and immediately titrated, 318; (2) dissolved in warm base, titrated after 15 min., 261; (3) in warm base after 2·5 hr., 248; (4) refluxed in base for 13 hr., 166. On storage at room temperature, the substance lost its lustre and crumbled, and then had m. p. 58—70°.

Neutral Fraction from Clovene Oxidation.—The neutral material (63 g.) resulting from several oxidations of ordinary clovene with chromium trioxide was fractionated to give, along with much unchanged clovene, a fraction, b. p. 116—130°/1·3 mm., that contained ketonic material (20 g.). This was redistilled at 1·2 mm., and a fraction, b. p. 110·5—115°, $n_D^{25\cdot0}$ 1·5039, was taken (5·6 g.). The ketone formed an orange 2 : 4-*dinitrophenylhydrazone*, m. p. 194—196° (from methanol) (Found: C, 63·3; H, 6·4; N, 14·0. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·1%).

Clovenic Glycol.—Lithium aluminium hydride (49 g.) was slurried with absolute ether (2 l.) in a 5-l. flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. The dropping funnel contained powdered clovenic acid (76 g.) and anhydrous ether (500 ml.). The acid was kept in suspension by constant stirring, and the mixture was added to the reductant as fast as the reaction permitted. A second charge of clovenic acid (76 g.) in ether (500 ml.) was then added, and the mixture was refluxed for 34 hr. The excess of lithium aluminium hydride was then decomposed cautiously with water, and the whole acidified with 10% sulphuric acid. The ether layer was separated, the water layer was extracted twice with ether, and the combined ethereal extracts were washed several times with saturated sodium hydrogen carbonate solution, and then water. After drying and evaporation, a colourless gum remained. A portion of this *clovenic glycol* was distilled with great difficulty owing to the immobility of the substance, b. p. 140—142°/0·10 mm., $n_D^{25\cdot0}$ 1·5108 (Found: C, 74·7; H, 11·6. $C_{15}H_{28}O_2$ requires C, 74·95; H, 11·7%). The *diphthalate* was prepared by refluxing the glycol (0·5 g.) with phthalic anhydride (0·8 g.) in toluene (5 ml.) for 12 hr., and chilling the reaction mixture; it had m. p. 184—185° (from ethyl acetate) (Found: C, 69·4; H, 7·0. $C_{31}H_{36}O_8$ requires C, 69·4; H, 6·8%).

Potassium Hydrogen Sulphate Dehydration of Clovenic Glycol.—The glycol (25 g.) was mixed with finely ground, freshly fused potassium hydrogen sulphate (75 g.) in a distillation flask and slowly heated under a pressure of 0·25 mm. A vigorous reaction ensued as water vaporised from the flask, and then a colourless mobile oil distilled at 90°. The yield of crude product was 20·6 g., or 89%. After being washed with bicarbonate solution, water, and dried in ethereal solution, the product was distilled through a 17-cm. Vigreux column and the main fraction, b. p. 92—97°/0·20 mm., was taken (15·1 g.). Refractionation of this gave the monodehydrated product, mainly *clovenic ether*. b. p. 95·5°/0·20 mm., m. p. 12·5°, $n_D^{25\cdot0}$ 1·4970 (Found: C, 81·3; H, 12·1. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%). Microhydrogenation, semiquantitative bromination, and acetylation proved the product to be inhomogeneous and to consist of about 10% of unsaturated alcohol mixed with 90% of inert ethereal material.

Oxidation of the Dehydration Mixture.—The oil (5 g.) in pyridine (35 ml.) and water (10 ml.) was warmed on the steam-bath while powdered potassium permanganate (9·5 g.) was added in portions. After 3 hr. the purple solution was diluted with water (100 ml.), and the excess of oxidant reduced with sulphur dioxide. After extraction of the solution with ether, the extract was washed several times with dilute hydrochloric acid, and then dilute potassium hydroxide. After drying, evaporation of the ether gave a yellow mobile oil (4·2 g.), which partly solidified. The solid, *clovenic lactone* recrystallised from light petroleum as white prisms, m. p. 93·0—94·5° (Found: C, 76·45; H, 10·3. $C_{15}H_{24}O_2$ requires C, 76·2; H, 10·2%). The lactone was inert to boiling 15% potassium hydroxide solution, and to chromium trioxide in acetic acid for 42 hr.

Distillation of the neutral oil (from which the lactone had solidified) revealed it to be mainly unchanged clovenic ether.

The acidic constituent (0·4 g.) from the above oxidation (obtained from the potassium hydroxide washings) was recrystallised from hexane–ethanol, to give fibrous needles of a *keto-dicarboxylic acid*, m. p. 178·5—180·0° (Found: C, 60·9; H, 7·8; equiv., 136·7. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9%; equiv., 128·2).

Dehydration by Sulphuric Acid.—Clovenic glycol (6·8 g.) was mixed with concentrated sulphuric acid (0·82 g., or 12% by wt.), and toluene-*p*-sulphonic acid (0·55 g., 8% by wt.) in 15 ml. of toluene, and refluxed for 15 hr. The dark product was neutralised with carbonate solution, and the aqueous layer was extracted with toluene. After washing with water and drying, evaporation *in vacuo* gave 6·3 g. of dark brown mobile oil. Careful fractional distillation (Vigreux column) at 2·5 mm., gave a colourless product (2·5 g.), b. p. 113—114·5°, $n_D^{25\cdot0}$ 1·4964. A specimen of this monodehydrated *product* had b. p. 114°, $n_D^{25\cdot0}$ 1·4980 (Found: C, 81·2; H, 11·6. $C_{15}H_{26}O$ requires, C, 81·0; H, 11·8%). Microhydrogenation and quantitative bromination revealed the presence of 19% of an unsaturated constituent, the remainder being a saturated compound *not* identical with clovenic ether since oxidation with permanganate in pyridine gave as the main product a neutral light oil that refused to crystallise, together with a *diketo-dicarboxylic aicd*, whose m. p. (from ethyl acetate) was not reproducible (234—235° up to 249—251°; Fisher–Johns m. p. block) [Found: C, 59·9; H, 8·0%; *M* (Rast), 292; equiv., 148. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%; *M*, 300; equiv., 150].

A portion (4·47 g.) of the above dehydration mixture was treated with chromium trioxide (5·4 g.) in acetic acid (25 ml.) (containing a little water) at 40° for 27 hr. and set aside for 4 days. This yielded mainly neutral material containing starting material, together with a trace of a ketone that furnished a solid 2 : 4-dinitrophenylhydrazone in microscopic quantities. A solid degraded *keto-dicarboxylic acid* (0·47 g.) was also formed, having m. p. 212·5—213·5° (from ethyl acetate) (Found: C, 61·9; H, 8·2%; equiv., 135. $C_{14}H_{22}O_5$ requires C, 62·2; H, 8·2%; equiv., 135).

Dehydration with Formic Acid.—Clovenic glycol (33 g.) was refluxed for about 7 hr. with 90% formic acid (300 ml.). After the usual working up there was obtained a monodehydration *product* (5·2 g.), b. p. 93—94°/1·2 mm., $n_D^{25\cdot0}$ 1·4941 (Found: C, 81·4; H, 11·4. $C_{15}H_{26}O$ requires C, 81·0; H, 11·8%), together with *clovenic glycol monoformate* (22 g.), b. p. 138°/0·7 mm., $n_D^{25\cdot0}$ 1·4989 (Found: C, 72·3; H, 9·95. $C_{16}H_{28}O_3$ requires C, 71·6; H, 10·5%). Hydrolysis of the monoformate with hot 10% aqueous sodium hydroxide readily yielded clovenic glycol, identified through the diphthalate.

Oxidation of the monodehydration product (2·0 g.) with potassium permanganate (3·8 g.) in pyridine (60 ml.) at 50° for 24 hr. yielded a thin neutral oil (1·15 g.), saturated to bromine and inert to 2 : 4-dinitrophenylhydrazine and to boiling 20% aqueous sodium hydroxide, together with a trace of *diketo-dicarboxylic acid*, prisms (from ethyl acetate), m. p. variable, 243—244°, 245—247° (Found: C, 59·8; H, 8·1. $C_{15}H_{24}O_6$ requires C, 60·0; H, 8·1%). A mixed m.p. of this acid with the above diketo-dicarboxylic acid was 236—237°.

Dehydration with Phosphoric Oxide.—Clovenic glycol (15 g.) was warmed to 50° and phosphoric oxide (13 g.) added portionwise while the temperature of the reactants rose to 100°, despite ice-cooling. After the usual working-up the crude product (10·4 g.) was fractionated (Vigreux column) at 4 mm., to yield a fraction, b. p. 105—107°, $n_D^{25\cdot0}$ 1·4955 (0·45 g.), which contained mainly doubly unsaturated material (carbon and hydrogen total, 97·3%), although this could not be obtained pure. Bromination formed an unstable bromide. The main fraction (3·41 g.) had b. p. 108—122°/4 mm., $n_D^{25\cdot0}$ 1·5001, and on oxidation with chromium trioxide gave largely neutral products that were not further studied.

Clovane (XIII).—Pure clovene (4·3 g.), obtained from clovene dibromide (m. p. 71·0—71·5°), was hydrogenated at 1 atm. in glacial acetic acid (20 ml.) with Adams catalyst (50 mg.) (uptake 99·3%). Fractional distillation at 12 mm. gave *clovane* as the only fraction, b. p. 115°, $n_D^{25\cdot0}$ 1·4863, $[\alpha]_D^{26\cdot0}$ −5·1° (in $CHCl_3$; *c* 5·13) (Found: C, 87·4; H, 12·7. $C_{15}H_{26}$ requires C, 87·3; H, 12·7%).

The $C_{15}H_{26}O_2$ *Glycol* (XI).—Caryophyllene (100 g.) was added dropwise to a stirred mixture of 90% formic acid (750 ml.) and 30% hydrogen peroxide (150 ml.) at such a rate that the temperature remained at 40—50° (5 hr.). Then the clear yellow solution was kept at 40° for an additional hour, and at room temperature for 4 hr. The formic acid was removed *in vacuo*, and the residue refluxed for 9 hr. with 10% sodium hydroxide solution, and then steam-distilled until 10 l. of distillate had formed. The non-volatile residue was taken up in ether, washed, treated with charcoal, and evaporated to a gum. Crystallisation from the minimum amount of ethyl acetate gave 25 g. of crude glycol; several recrystallisations from benzene furnished 16·5 g. of pure 4 : 4 : 8-*trimethyl*tricyclo[6 : 3 : 1 : $0^{1:5}$]*dodecane*-2 : 9-*diol*, m. p. 152—153° (Found: C, 75·7; H, 10·9. $C_{15}H_{26}O_2$ requires C, 75·6; H, 11·0%). The *mono*-3 : 5-*dinitrobenzoate*, readily formed in pyridine with one equivalent of reagent, had m. p. 214·0—215·5° (from acetone) (Found: C, 61·4; H, 6·7; N, 6·5. $C_{22}H_{28}O_7N_2$ requires C, 61·1; H, 6·5; N, 6·5%).

The $C_{15}H_{24}O_2$ *Tricyclic Ketone* (XII).—The glycol (16·5 g.) in glacial acetic acid (75 ml.) was treated with chromium trioxide (9·3 g.) in aqueous acetic acid, the temperature being kept below 25°. Next morning the mixture was diluted with water and extracted many times with ether, and the extracts were washed with carbonate solution. Evaporation left a thick oil that crystallised spontaneously. Recrystallisation from hexane and from ethanol–water gave 9 g. of pure 4 : 4 : 8-trimethyl*tricyclo*[6 : 3 : 1 : $0^{1:5}$]dodecane-2 : 9-dione (XII), m. p. 50—51°, analysed as the *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 228—232·5° (decomp.) (Found: C, 54·4; H, 5·25; N, 18·8. $C_{27}H_{30}O_8N_8$ requires C, 54·5; H, 5·1; N, 18·85%). Acidification of the carbonate washings furnished a thick oil (1·54 g.) that solidified. Recrystallisation from ethyl acetate gave prisms, m. p. 230—231·5°, of 5-*carboxy*-1 : 1 : 5-*trimethyl*-3-*oxohexahydroindan*-9-*yl-acetic acid* (Found : C, 63·65; H, 7·8%; equiv., 139. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·9%; equiv., 141).

Clovane from the Tricyclic Diketone.—The diketone (9 g.) in diethylene glycol (100 ml.) was refluxed with potassium hydroxide (13 g.) and hydrazine hydrate (10 ml.; 85%) for 1·5 hr. Then, following Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487), the water was distilled off, and the mixture refluxed for 4 hr. The product was extracted in ether, washed, dried, and after removal of the ether, distilled from metallic sodium, yielding 6·02 g. (76·2%) of clovane, b. p. 115°/12 mm., $n_{\mathrm{D}}^{25\cdot0}$ 1·4865, $[\alpha]_{\mathrm{D}}^{26\cdot0}$ −5·3° (in $CHCl_3$; *c* 5·12) (Found : C, 87·45; H, 12·8%).

pseudo*Clovene*.—β-Caryophyllene alcohol (265 g.) was dehydrated as described by Henderson, McCrone, and Robertson (*loc. cit.*) to give a 95·5% yield of crude product. Distillation at 1·5 mm. gave 220 g., b. p. 85—93°; redistillation through the Stedman column yielded crude *pseudo*clovene, b. p. 112—124°/12·0 mm., $\alpha_{\mathrm{D}}^{25\cdot0}$ +13·25° to +10·74°, and crude *iso*clovene, b. p. 125—127°, $\alpha_{\mathrm{D}}^{25\cdot0}$ −0·83° to −46·46°. Refractionation of *pseudo*clovene gave, as the best fraction, b. p. 119·6°/12·0 mm., $n_{\mathrm{D}}^{25\cdot0}$ 1·4928, $\alpha_{\mathrm{D}}^{25\cdot0}$ +17·70°, although a fraction, b. p. 113·7°, $n_{\mathrm{D}}^{25\cdot0}$ 1·4890, $\alpha_{\mathrm{D}}^{25\cdot0}$ +13·40°, gave an infra-red spectrum identical with that of the higher-boiling specimen.

*pseudo*Clovene readily absorbed bromine, with liberation of some hydrogen bromide, but the product gave off large volumes of hydrogen bromide at room temperature. With *N*-bromo-succinimide substitution readily occurred, but isolation of the product was accompanied by the loss of much hydrogen bromide.

Oxidation of *pseudo*clovene (similar to that of clovene) with ozone yielded the oily dibasic *pseudo*clovenic acid, purified as *dimethyl* pseudo*clovenate*, b. p. 112°/0·05 mm., $n_{\mathrm{D}}^{25\cdot0}$ 1·4759 (Found : C, 68·8; H, 9·5. $C_{17}H_{28}O_4$ requires C, 68·9; H, 9·5%). *Dimethyl dibromo*pseudo*clovenate*, b. p. (bath temp.) 60°/10^{-3} mm. (Found : Br, 35·9. $C_{17}H_{26}O_4Br_2$ requires Br, 35·2%), was prepared from the acid (12·6 g.), phosphorus pentachloride (21·6 g.), and bromine (18·5 g.) that had been dried over phosphoric oxide; the mixture was warmed with an infra-red lamp, and after being kept overnight was treated with methanol.

Dehydration of β-Caryophyllene Alcohol with Sulphuric Acid.—The alcohol (15 g.) was dissolved in ether (50 ml.), and concentrated sulphuric acid (20 ml.) was added dropwise, the temperature reaching 50°. The mixture was then warmed on the water-bath for 1 hr. at 75°. The products were poured into water, neutralised with 20% sodium hydroxide solution, and extracted with ether. The product was an oil (10 g., 72·5%), which when fractionated from sodium through a Vigreux column gave as one fraction, b. p. 120—121°/13 mm., $n_{\mathrm{D}}^{25\cdot0}$ 1·4865, $[\alpha]_{\mathrm{D}}^{27\cdot5}$ −30·6° (in $CHCl_3$; *c* 3·53), a mixture (Found : C, 87·2; H, 12·6. Calc. for $C_{15}H_{26}$: C, 87·3; H, 12·7%) of saturated (mainly) and unsaturated material. Quantitative hydrogenation showed the mixture to contain 28·2% of unsaturated constituent.

Oxidation of the Dehydration Mixture.—The above mixture (6·1 g.) in glacial acetic acid (75 ml.) was treated with chromium trioxide (8·0 g.) in acetic acid (25 ml.) containing 2 ml. of water. After 2 hr. at 65—70°, the mixture was worked up to yield an acid (2·5 g.) and a neutral fraction (3·6 g.). The acid was esterified with diazomethane, furnishing the ester, b. p. 125—127°/1·0 mm., $n_{\mathrm{D}}^{25\cdot0}$ 1·4725, of a keto-acid (Found : C, 70·2; H, 9·9. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·1%). The neutral fraction was proved to be β-caryophyllene alcohol by direct comparison with authentic material.

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