# *The Caryophyllenes. Part X.* Oxides from the Caryophyllenes.*

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The systematic degradation of one caryophyllene oxide and two *iso*caryophyllene oxides has given, from each, the same monoketone $C_{14}H_{24}O$, keto-acid $C_{11}H_{18}O_3$, and dicarboxylic acid $C_{12}H_{20}O_4$. This, together with other considerations which are discussed, supports a *trans*-configuration of the endocyclic double bond (cf. I) for caryophyllene (*i.e.*, β-caryophyllene) and the corresponding *cis*-arrangement (II) for *iso*caryophyllene (*i.e.*, γ-caryophyllene).

After the establishment of the carbon skeleton of caryophyllene (Šorm, Dolejš, and Plíva, *Coll. Czech. Chem. Comm.*, 1950, **15**, 186; Barton and Lindsey, *Chem. and Ind.*, 1951, 313; *J.*, 1951, 2988; Dawson, Ramage, and Wilson, *Chem. and Ind.*, 1951, 464; Dawson and Ramage, *J.*, 1951, 3382), evidence has been provided in support of formula (III) (Barton, Bruun, and Lindsey, *Chem. and Ind.*, 1951, 910; 1952, 691; *J.*, 1952, 2210; Robertson and Todd, *Chem. and Ind.*, 1953, 437; Atwater and Reid, *ibid.*, p. 688).

In agreement with Aebi, Barton, and Lindsey (*J.*, 1953, 3124) it is considered that the names β-caryophyllene and γ-caryophyllene are now best replaced by caryophyllene and *iso*caryophyllene respectively. These authors have shown the two hydrocarbons to be geometrically isomeric about the endocyclic double bond by rearrangements involving the conversion of their oxides (IV) into the same tricyclic diketone (VI). Caryophyllene and *iso*caryophyllene were considered by them to be the *trans*- (I) and the *cis*-isomer (II) respectively since Prelog, Schenker, and Küng (*Helv. Chim. Acta*, 1953, **36**, 471) have shown that the rate of reaction with per-acid is greater for *trans*- than for *cis-cyclo*nonene. Moreover, the strained *trans*-form for caryophyllene allowed its conversion into the strain-free *cis*-form by the action of nitrous acid and made it possible that the nitrosochlorides of both caryophyllenes could yield the same nitrolbenzylamine.

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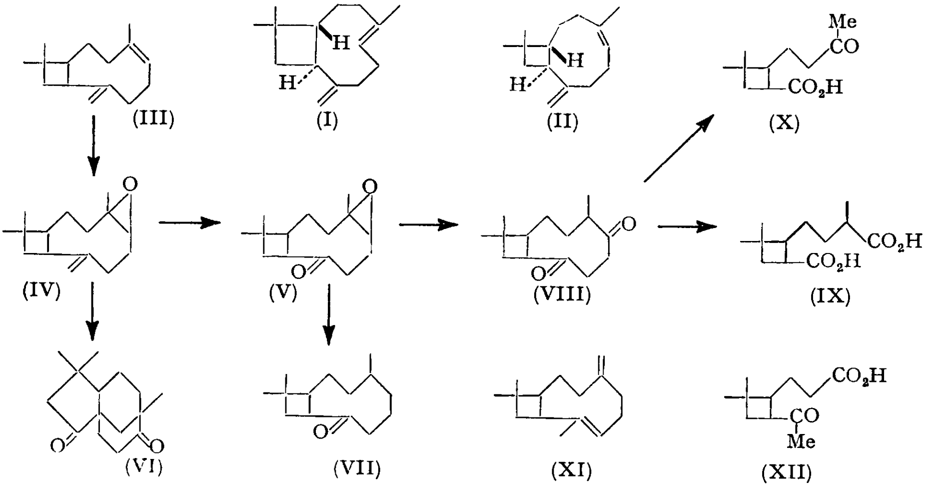
* Part IX, *J.*, 1951, 3382.

These general conclusions were fully supported by the present work which provided direct evidence of geometrical isomerism by an examination of the oxidative degradation products of caryophyllene and *iso*caryophyllene. Treibs (*Chem. Ber.*, 1947, **80**, 56) had prepared the crystalline caryophyllene oxide, which on further oxidation gave the epoxy-ketone. Two products resulted from the high-pressure reduction of the latter compound. One was described as a saturated monoketone $C_{14}H_{26}O$ whilst the other, on oxidation, gave a liquid diketone $C_{14}H_{22}O_2$. This series of reactions has been re-examined, by employing an oxide prepared from caryophyllene with the readily available monoperphthalic acid and oxidising the product, from the high-pressure reduction, with chromic acid, before fractionation. This was necessary since it was not known whether the carbonyl group in the epoxy-ketone was completely reduced under the conditions employed. The subsequent oxidation with chromic acid ensured that this group was re-formed and, at the same time, oxidised any secondary alcohol resulting from the opening of the oxide ring. Two fractions were isolated, one of which gave the diketone, now obtained crystalline, m. p. 53°. The lower-boiling fraction was found to be a monoketone $C_{14}H_{22}O$ (VII), which was characterised by the preparation of its crystalline 2 : 4-dinitrophenylhydrazone and 4-phenylsemicarbazone. The structure of the diketone was proved to be (VIII) by further degradation with selenium dioxide followed by permanganate, which afforded a keto-acid $C_{11}H_{18}O_3$ together with a dicarboxylic acid (IX). The latter was shown to have the composition $C_{12}H_{20}O_4$ by the preparation of a dianilide and di-*p*-phenylphenacyl ester. The keto-acid was identical with a degradation product from caryophyllene, the structure of which had been established as (X) by Dawson and Ramage (*loc. cit.*). This series of reactions provided proof of the oxide structure (IV) and supported formula (III) for caryophyllene. Our alternative formulation (XI) (Dawson, Ramage, and Whitehead, *Chem. and Ind.*, 1952, 450) which would require (XII) as the keto-acid is no longer tenable.



The same procedure was followed with *iso*caryophyllene, which on treatment with monoperphthalic acid gave a crystalline oxide-*a*. The reaction proceeded slowly and it was evident that the yield was poor compared with that for caryophyllene oxide. Fractionation of the mother-liquors gave a liquid oxide-*b* which was kept cold to allow the oxide-*a* to separate as far as possible; both oxides were obtained in about the same yield. Each gave a different crystalline epoxy-ketone on further oxidation, although the product from oxide-*a* was of somewhat indefinite melting point. It was evident that *iso*caryophyllene gave rise to two oxides but careful examination of the product from caryophyllene showed no indication of a second oxide in this case, the pure crystalline oxide being, available in almost 80% yield.

After high-pressure reduction and subsequent oxidation with chromic acid, each of the *iso*caryophyllene epoxy-ketones gave two ketonic fractions. In each case the lower-boiling fraction was identical with the monoketone (VII) previously obtained in the caryophyllene oxide series. The diketone fraction crystallised readily, whether from oxide-*a* or -*b*, and had m. p. 71°, whereas the earlier diketone had m. p. 53°. However, the diketones were certainly structurally similar since, by following the above degradation procedure, the diketone, m. p. 71°, gave the keto-acid $C_{11}H_{18}O_3$ and dicarboxylic acid $C_{12}H_{20}O_4$ obtained previously. Hence each of the three oxides gave as degradation products the same bicyclic monoketone (VII), together with the same keto-acid $C_{11}H_{18}O_3$ (X), and the same dicarboxylic acid $C_{12}H_{20}O_4$ (IX). The parent hydrocarbons must therefore be geometrically isomeric about the endocyclic double bond. An examination of models supported the view that the compact *trans*-configuration (I) could be sterically hindered in the per-acid reaction, which would account for isolation of only one form of caryophyllene oxide. The more open *cis*-configuration (II) for *iso*caryophyllene would readily allow the formation of two oxides and two epoxy-ketones, which would be stereoisomeric with respect to the epoxide ring and the adjoining methyl group.

In order to account for the products formed in the pressure hydrogenation at 100°/80 atm., it was considered that the oxide ring would open, giving both tertiary and secondary alcohols. The former would then produce the same monoketone from each of the three oxides. From the secondary alcohols, the formation of different diketones (VIII) may arise from the opening of the oxide ring with racemisation, at the carbon atom carrying the methyl group, for the open *iso*caryophyllene oxides, and without racemisation for the hindered caryophyllene oxide.

Although Robertson and Todd (*loc. cit.*) established a *trans*-union of the rings for caryophyllene there is, as yet, no evidence for the configuration in the monoketone and diketones described.

## EXPERIMENTAL

Light petroleum refers throughout to the fraction of b. p. 40—60°. All rotations are for methanol solution.

iso*Caryophyllene Oxides*-a *and* -b.—*iso*Caryophyllene was recovered from them other-liquors remaining after the preparation of caryophyllene nitrosite (Deussen and Lewinsohn, *Annalen*, 1907, **356**, 1) and was also obtained from the nitrosite by boiling with alcohol (*idem, ibid.*, 1908, **359**, 245).

The hydrocarbon (50·6 g., from either route) was treated at 0°, with gentle stirring with an ethereal solution of monoperphthalic acid (45·3 g.; equimol. amounts taken after volumetric analysis of the per-acid). After the initial reaction had ceased, as denoted by precipitation of phthalic acid, the mixture was set aside at room temperature for 48 hr. The ethereal solution was decanted, washed with sodium carbonate solution, dried, and evaporated. The product (51·1 g.), when kept in the refrigerator, partially crystallised. After filtration, the crystals were washed with a little ice-cold light petroleum and the process of cooling repeated with the filtrate. *iso*Caryophyllene oxide-*a* (15 g.) crystallised from light petroleum in large prisms, m. p. 77°, $[\alpha]_D^{19}$ $-5°$ (*c*, 1·94) (Found: C, 82·2; H, 11·0. Calc. for $C_{15}H_{24}O$: C, 81·8; H, 11·0%). The m. p. was not raised on repeated crystallisation from light petroleum or by chromatography on alumina; Aebi, Barton, and Lindsey (*loc. cit.*) record m. p. 80—81°. The filtrate and washings were fractionated in a Towers column and gave (i) unchanged *iso*caryophyllene (8·8 g.), b. p. 115—128°/12 mm., $n_D^{21}$ 1·4945, (ii) an oil (21·2 g.), b. p. 137—145°/12 mm., and (iii) undistilled residue (7 g.). On strong cooling, fraction (ii) gave a little oxide-*a* and the remainder distilled and gave iso*caryophyllene oxide*-b, b. p. 136—138°/12 mm., $n_D^{20}$ 1·4918, $d_{19}^{19}$ 0·9795, $[\alpha]_D^{18}$ $+23°$ (*c*, 2·300) (Found: C, 81·4; H, 10·9. $C_{15}H_{24}O$ requires C, 81·8; H, 11·0%). Oxide-*a* (17·5 g.) and -*b* (18·2 g.) were obtained in 32 and 34% yield respectively.

*Caryophyllene Oxide.*—Caryophyllene (48·8 g., from Messrs. W. J. Bush and Co. Ltd.) by the above procedure, except that the reaction was complete after 24 hr., gave recovered caryophyllene (6·6 g.) and a fraction, b. p. 136—142°/12 mm., crystallisation of which from methanol gave caryophyllene oxide (37·5 g., 77%) in large prisms, m. p. 63—64°, $[\alpha]_D^{19}$ $-62°$ (*c*, 1·98).

*Permanganate Oxidation of* iso*Caryophyllene Oxide*-a.—The oxide-*a* (20 g.) was oxidised in acetone (200 c.c.) containing water (2 c.c.) with potassium permanganate (40 g., 60 mesh) added in small portions during 48 hr., with stirring and water-cooling. The whole was filtered and the sludge washed well with acetone. The solvent was removed from the filtrate and the residue (12·5 g.), after being taken up in ether and filtered from any remaining manganese dioxide, gave on fractionation (i) unchanged oxide-*a* (4·2 g.), b. p. 120—130°/2 mm., and (ii) epoxy-ketone-*a* (6·7 g.), b. p. 135—145°/2 mm. With 2 : 4-dinitrophenylhydrazine the former gave a ***derivative***, m. p. 185°, from ethanol, corresponding to the opening of the oxide ring; this was also prepared from oxide-*a* (Found : C, 62·8; H, 7·1. $C_{21}H_{28}O_4N_4$ requires C, 62·9; H, 7·1%). The ***epoxy-ketone***-a crystallised in the refrigerator and the solid was recrystallised from methanol containing a little water, forming plates, m. p. 31—34°, b. p. 140°/3 mm., $[\alpha]^{21}_{D}$ −72° (*c*, 2·332) (Found : C, 75·5; H, 9·5. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). The ***semicarbazone***, m. p. 209°, crystallised with difficulty from aqueous ethanol (Found: C, 64·4; H, 8·9. $C_{15}H_{25}O_2N_3$ requires C, 64·5; H, 9·0%). Shaking with sulphuric acid (0·1N; 40 c.c.) and light petroleum (50 c.c.) for 6 hr. hydrolysed the semicarbazone (0·5 g.) but the recovered ketone, after crystallising from aqueous methanol, still melted over the range 31—34°.

The sludge from the oxidation was suspended in water (600 c.c.), and the manganese dioxide dissolved by an excess of sulphur dioxide, before further acidification and extraction with ether. Removal of the solvent gave a product (6·7 g.) which crystallised when shaken with a little ether and was separated into two isomeric hydroxy-acids. A portion of the crude acid (0·75 g.) was crystallised from monochlorobenzene (150 c.c.), and the product, m. p. 215—216°, further crystallised from the same volume of solvent. Pure ***hydroxy-acid*** separated in small opaque needles, m. p. 218°, $[\alpha]^{21}_{D}$ +46° (*c*, 0·821) (Found : C, 66·8; H, 8·8. $C_{15}H_{24}O_4$ requires C, 67·1; H, 9·0%). The filtrates were combined, the solvent distilled under reduced pressure, and the residue, crystallised from benzene, gave an isomeric ***hydroxy-acid*** in long colourless needles, m. p. 227°, $[\alpha]^{20}_{D}$ +53° (*c*, 0·647) (Found : C, 67·4; H, 8·8%). The latter acid (1 g.) was refluxed in dry benzene (100 c.c.) for 4 hr. with lead tetra-acetate (3 g.). Lead acetate was precipitated and, after cooling, filtered off, and the benzene solution washed with aqueous sodium carbonate. Removal of the benzene gave a neutral ***product*** (0·75 g.) which crystallised from *cyclo*hexane in prisms, m. p. 159° (Found : C, 68·4; H, 9·3. $C_{16}H_{26}O_4$ requires C, 68·1; H, 9·3%). As well as the expected conversion of the hydroxy-acid group into a carbonyl group, it is considered that the epoxide ring has been opened with the addition of acetic acid.

From the sodium carbonate extract, hydroxy-acid (0·2 g.) was recovered.

*Permanganate Oxidation of* iso*Caryophyllene Oxide*-b.—The oxide-*b* (20 g.) was oxidised by the above procedure and the neutral product on fractionation gave unchanged oxide-*b* (4 g.), b. p. 120—130°/2 mm., and iso***caryophyllene epoxy-ketone***-b (9·2 g.), b. p. 135—145°/2 mm., which solidified and then crystallised from light petroleum in long needles, m. p. 78—79°, $[\alpha]^{15}_{D}$ −13° (*c*, 1·978) (Found : C, 75·7; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). The ***semicarbazone***, m. p. 216°, crystallised readily from ethanol (Found : C, 64·7; H, 9·1. $C_{15}H_{25}O_2N_3$ requires C, 64·5; H, 9·0%). The ketone recovered from the semicarbazone had m. p. 78—79°.

From the sludge the acid (5·3 g.) was recovered as an oil.

*Permanganate Oxidation of Caryophyllene Oxide.*—The oxide (20 g.) when oxidised as for oxide-*a* above gave (i) unchanged oxide (7·15 g.), b. p. 135—149°/12 mm., and (ii) epoxy-ketone (6·1 g.), b. p. 154—158°/12 mm., which after several crystallisations from light petroleum had m. p. 60°. The semicarbazone had m. p. 235° as recorded by Barton and Lindsey (*loc. cit.*).

The acid product (3·4 g.) was obtained as a viscous oil and was converted into its methyl ester but gave no distinct fraction on distillation.

*Hydrogenation of the Epoxy-ketones.*—(*A*) *iso*Caryophyllene epoxy-ketone-*a* (6 g.) in methanol (250 c.c.) was hydrogenated for 8 hr. at 100°/80 atm. in the presence of Raney nickel (6 c.c. of settled suspension). After removal of the catalyst and solvent the residue (6·1 g.) in acetic acid (50 c.c.) was treated dropwise with chromium trioxide (3·3 g.) in water (3 c.c.) and acetic acid (5 c.c.) with ice-cooling. After 14 hr. at room temperature the product, isolated with ether, on fractionation gave (i) (1·55 g.), b. p. 108—120°/0·3 mm., $n^{19}_{D}$ 1·4840 and (ii) (3·15 g.), b. p. 125—140°/0·3 mm., $n^{19}_{D}$ 1·4903. The former yielded a monoketone, b. p. 145—147°/20 mm., $n^{22}_{D}$ 1·4813, $d^{16}_{16}$ 0·9489, $[\alpha]^{21}_{D}$ −33° (*c*, 2·144) (Found : C, 80·4; H, 11·5. Calc. for $C_{14}H_{24}O$ : C, 80·7; H, 11·6%). The 4-phenylsemicarbazone, m. p. 182° (Found : C, 74·3; H, 9·1. Calc. for $C_{21}H_{31}ON_3$ : C, 73·9; H, 9·2%), and 2 : 4-dinitrophenylhydrazone, m. p. 147° (Found : C, 61·7; H, 7·2. Calc. for $C_{20}H_{28}O_4N_4$ : C, 61·8; H, 7·3%), were identical with the corresponding derivatives (see following paper) from dihydrocaryophyllene-*b* and from the epoxy-ketone-*b* and caryophyllene epoxy-ketone (below). The second fraction solidified and after crystallisation from light petroleum, by strong cooling, gave iso***caryophyllene diketone*** (2·1 g.), m. p. 71°, $[\alpha]^{22}_{D}$ −50° (*c*, 2·180) (Found : C, 76·1; H, 10·0. $C_{14}H_{22}O_2$ requires C, 75·6; H, 10·0%). The ***monosemicarbazone***, prepared in cold aqueous alcohol, crystallised from aqueous ethanol (3 : 1) in colourless needles, m. p. 168° (Found : C, 64·4; H, 9·1. $C_{15}H_{25}O_2N_3$ requires C, 64·5; H, 9·0%), identical with the product prepared as below.

(*B*) *iso*Caryophyllene epoxy-ketone-*b* (5 g.) was similarly hydrogenated and the product (5·1 g.) oxidised (2·7 g. chromium trioxide) and gave fractions (i) (1·8 g.), b. p. 110—125°/0·4 mm., $n_D^{21}$ 1·4854, and (ii) (2·1 g.), b. p. 130—145°/0·4 mm., $n_D^{21}$ 1·4889. The former gave the monoketone, b. p. 146—148°/20 mm., $n_D^{17}$ 1·4840, $d_{16}^{16}$ 0·9499, $[\alpha]_D^{21}$ −35° (*c*, 2·212) (Found : C, 80·5; H, 11·2%), the 4-phenylsemicarbazone, m. p. 182° (Found : C, 74·3; H, 8·9%), and the 2 : 4-dinitrophenylhydrazone, m. p. 147° (Found : C, 61·3; H, 7·2%). The m. p.s were not depressed on admixture with the corresponding derivatives from the epoxy-ketone-*a* or from caryophyllene epoxy-ketone. The second fraction gave the *iso*caryophyllene diketone, m. p. 71°, $[\alpha]_D^{22}$ −47° (*c*, 5·10) (Found : C, 75·7; H, 9·6%), and monosemicarbazone, m. p. 168°, both of which were identical with the corresponding derivatives from the epoxy-ketone-*a*.

(*C*) Caryophyllene epoxy-ketone (10 g.) on reduction and subsequent oxidation (5·4 g. of chromium trioxide) gave the fractions (i) (2·5 g.), b. p. 110—125°/0·5 mm., and (ii) (5·35 g.), b. p. 130—145°/0·5 mm. The former gave monoketone, b. p. 136—137°/12 mm., $n_D^{19}$ 1·4833, $d_{16}^{16}$ 0·9484, $[\alpha]_D^{19}$ −34° (*c*, 2·310) (Found : C, 80·2; H, 11·6%). The same 4-phenylsemicarbazone, m. p. 182° (Found : C, 73·7; H, 9·2%), and 2 : 4-dinitrophenylhydrazone, m. p. 147° (Found : C, 62·1; H, 7·1%), were obtained as previously. The second fraction crystallised in the refrigerator and after recrystallisation from light petroleum gave caryophyllene diketone, m. p. 53°, $[\alpha]_D^{22}$ −11° (*c*, 2·054) (Found : C, 75·9; H, 9·8. Calc. for $C_{14}H_{22}O_2$ : C, 75·6; H, 10·0%). The diketone was considered to be identical with the product described by Treibs (*loc. cit.*). In cold aqueous alcohol it gave a *monosemicarbazone* in colourless plates, m. p. 213° (Found : C, 64·8; H, 9·1. $C_{15}H_{25}O_2N_3$ requires C, 64·5; H, 9·0%).

In an attempt to convert the diketone, m. p. 53°, into the diketone, m. p. 71°, by very dilute alkaline treatment, more complex changes occurred which are being examined.

*Treatment of Diketones with Selenium Dioxide followed by Permanganate.*—(*A*) Caryophyllene diketone (5·0 g.; m. p. 53°) was heated under reflux with selenium dioxide (1·25 g.) in acetic acid (50 c.c.) for 1 hr. The precipitated selenium was filtered off and the filtrate diluted with water and extracted with ether. The extract was washed with aqueous potassium hydroxide, dried, and evaporated and the residual oil (4·7 g.) dissolved in acetone (150 c.c.). To the refluxing solution, potassium permanganate (19 g.) dissolved in a minimum amount of hot water was added dropwise. The mixture was decolorised with sulphur dioxide, acidified, and extracted with ether. The acid components were extracted into sodium carbonate solution, then recovered (2·25 g.) by ether and esterified with diazomethane. Separation of the esters by fractionation gave (i) (0·9 g.), b. p. 100—110°/0·5 mm., $n_D^{21}$ 1·4490, and (ii) (1·1 g.), b. p. 115—130°/0·5 mm., $n_D^{21}$ 1·4511. The former was identified as the methyl ester of the keto-acid $C_{11}H_{18}O_3$ by the preparation of a semicarbazone, m. p. 137° (Found : C, 58·3; H, 8·4. Calc. for $C_{13}H_{23}O_3N_3$ : C, 58·0; H, 8·6%) not depressed on admixture with a sample prepared from caryophyllene nitrosite. The ester (0·2 g.) was hydrolysed with methanolic potassium hydroxide, and the resulting keto-acid characterised by the preparation of a semicarbazone, m. p. 187° (Found : C, 56·9; H, 8·4. Calc. for $C_{12}H_{21}O_3N_3$ : C, 56·5; H, 8·3%), identical with the semicarbazone of the keto-acid $C_{11}H_{18}O_3$.

The second fraction was hydrolysed with methanolic potassium hydroxide, and the recovered liquid acid characterised by the formation of a *di*-p-*phenylphenacyl ester*, m. p. 83° (Found : C, 77·9; H, 6·6. $C_{40}H_{40}O_6$ requires C, 77·9; H, 6·5%), and a *dianilide* which crystallised from aqueous alcohol in long colourless needles, m. p. 192° (Found : C, 76·2; H, 7·9. $C_{24}H_{30}O_2N_2$ requires C, 76·2; H, 8·0%).

The neutral product (about 1·7 g.) from this and the following oxidation is being examined.

(*B*) *iso*Caryophyllene diketone (5·0 g., m. p. 71°) by the selenium dioxide and permanganate procedure gave (i) methyl ester of the keto-acid $C_{11}H_{18}O_3$ (0·7 g.), b. p. 100—105°/0·5 mm., $n_D^{17}$ 1·4508, and (ii) dicarboxylic ester (1·0 g.), b. p. 115—130°/0·5 mm., $n_D^{17}$ 1·4580. The former gave the same semicarbazone, m. p. 136°, as above (Found : C, 58·1; H, 8·5%) and after hydrolysis gave the semicarbazone, m. p. 188° (Found : C, 56·7; H, 8·4%). Fraction (ii) afforded a dicarboxylic acid, characterised by the preparation of a di-*p*-phenylphenacyl ester, m. p. 83° (Found : C, 78·2; H, 6·5%), and dianilide, m. p. 192°. The derivatives described were identical with the corresponding products from caryophyllene diketone.

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