

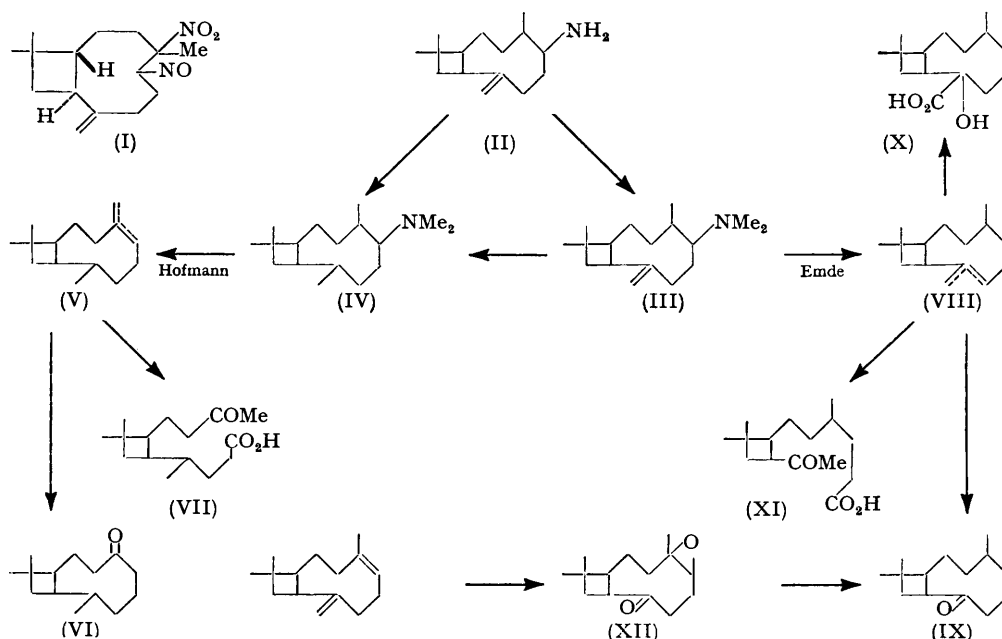
*The Caryophyllenes. Part XI.\* The Structure of Caryophyllene Nitrosite.*

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[Reprint Order No. 5424.]

Dihydrocaryophyllenes have been prepared from caryophyllene nitrosite by Hofmann and Emde degradations of dimethylamino-tetrahydro- and -dihydrocaryophyllene respectively. Oxidation of the dihydrocaryophyllene-*b* from the Emde route gave a saturated monoketone identical with the product obtained from the oxides of caryophyllene and *isocaryophyllene* (preceding paper) and established the structure of the nitrosite as (I).

THE characteristic blue nitrosite has been employed as a source of pure caryophyllene (Evans, Ramage, and Simonsen, *J.*, 1934, 1806) and its degradation was reported by Ramage and Simonsen (*J.*, 1935, 1581), but many facts (detailed then on p. 1583) were difficult to reconcile with the Ruzicka formulation. By reduction of the nitrosite with sodium and alcohol, aminodihydrocaryophyllene (Semmler and Mayer, *Ber.*, 1911, **44**, 3657) was available and offered a route to both possible dihydrocaryophyllenes. In this



way it was hoped to examine the relation of each of the caryophyllene double bonds to the ring system. Recent work on caryophyllene (for references, see preceding paper) would allow the aminodihydrocaryophyllene to be formulated as (II) on the assumption that nitrosite and oxide formation were concerned with the same endocyclic double bond.

Aminotetrahydrocaryophyllene was prepared from (II) by catalytic reduction and converted directly into the methiodide of the corresponding tertiary amine (IV). Alternatively, dimethylaminodihydrocaryophyllene (III) was obtained either by the action of excess of methyl iodide, followed by decomposition of the resulting methiodide by heat, or by treatment with formaldehyde. Hydrogenation of the double bond in the presence

\* Part X, preceding paper.

of palladium-charcoal gave the base (IV) which was then converted into the methiodide. A Hofmann reaction on the corresponding methohydroxide gave dihydrocaryophyllene-*a* (V) which must have the double bond in the same region as was associated with the formation of the nitrosite. Ozonolysis of (V) gave a neutral substance considered to be (VI) which formed only gums as carbonyl derivatives. Permanganate oxidation, however, gave a hydroxy-acid, a keto-acid (VII), and the corresponding keto-aldehyde, all formed without loss of carbon. The formation of the hydroxy-acid was comparable with that of nopinic acid from  $\beta$ -pinene (Wallach and Blumann, *Annalen*, 1907, **356**, 228). Oxidation of the hydroxy-acid by sodium bismuthate (Rigby, *J.*, 1950, 1907) gave more ketone (probably VI), from which no crystalline derivatives were obtained. Hypobromite oxidation of the keto-acid (VII) and keto-aldehyde, followed by further permanganate oxidation in the case of the aldehyde, gave a dicarboxylic acid, characterised as its dianilide.

The basic group was removed from (III) by Emde reduction of its methiodide, a modification of Groenewoud and Robinson's procedure (*J.*, 1934, 1692) being used. The yield of dihydrocaryophyllene-*b* (VIII) was improved by employing a large excess of sodium amalgam. Permanganate oxidation of (VIII) gave the ketone (IX) together with the hydroxy-acid (X), both corresponding to oxidation at an exocyclic double bond. The former was characterised by crystalline derivatives which were readily available. There was also obtained the keto-acid (XI) together with the corresponding keto-aldehyde, arising from oxidation at an endocyclic double bond. These observations on the double bond not concerned in the formation of the nitrosite served to exclude the Ruzicka formula. Sodium bismuthate oxidation proved the structure of the hydroxy-acid (X) by giving a further quantity of the ketone (IX), whilst the keto-acid (XI) on hypobromite treatment gave a dicarboxylic acid which formed a dianilide, m. p. 187°. By reducing technical caryophyllene with Raney nickel, Ruzicka and his co-workers (*Helv. Chim. Acta*, 1939, **22**, 716) obtained a dihydrocaryophyllene which was converted into a dicarboxylic acid having a dianilide, m. p. 188°. On ozonolysis, the dihydrocaryophyllene-*b* gave mainly the ketone (IX), some keto-aldehyde, and very little of the acid products.

The evidence from the oxidations of the dihydrocaryophylenes has necessitated bond mobility between the exocyclic and adjacent endocyclic positions, depending upon reaction conditions. A similar mobility was noted by Bradfield, Penfold, and Simonsen (*J.*, 1935, 309) for the oxidation of  $\beta$ -santalylmalonic acid. It was thought that the absence of crystalline derivatives from the ketone derived from dihydrocaryophyllene-*a* (contrast the ketone from -*b*) was due to *cis-trans*-isomerism at the ring junction. That this was not the case arose from the work developed in the preceding paper on the reductive elimination of the epoxide oxygen from the three epoxy-ketones of the form (XII). Each gave as one of the main products a ketone  $C_{14}H_{24}O$  (IX), the derivatives of which were identical with those available from the ketone derived from dihydrocaryophyllene-*b*. The structure (IX) was thereby established for the ketone from the Emde route and, hence, dihydrocaryophyllene-*b* must be represented as (VIII). A direct relation was thus established between the blue nitrosite and caryophyllene oxide and showed that the former was prepared by addition to the same double bond as was attacked by the per-acid; the suggestion (Dawson, Ramage, and Wilson, *Chem. and Ind.*, 1951, 464) that nitrosite formation involved addition to the exocyclic ethylenic linkage is therefore untenable. Barton, Bruun, and Lindsey (*J.*, 1952, 2214) as a result of infra-red measurements had established that the nitrosite retained the exocyclic methylene group.

Although (II) was known to contain stereoisomers (Evans, Ramage, and Simonsen, *loc. cit.*) these must depend only on the disposition of the amino-group, so that after the Emde reaction the resulting ketone (IX) was homogeneous and formed pure derivatives readily. The failure to obtain solid derivatives from the material assumed to be ketone (VI) may be due to further stereoisomers which arise on reduction of the double bond in (II) or (III).

An earlier attempt to relate the structure of the blue nitrosite to that of caryophyllene oxide was unsuccessful since the products from the action of per-acid on dihydrocaryophyllene-*a* and -*b* failed to crystallise after repeated fractionation, chromatography over alumina, or keeping. It was not possible, therefore, to relate the oxides available in this

way to the dihydro-oxides which had been prepared by direct reduction of caryophyllene and isocaryophyllene oxides. Two liquid oxides from a dihydrocaryophyllene, obtained by catalytic reduction of caryophyllene, have previously been reported by Rydon (*J.*, 1939, 537).

#### EXPERIMENTAL

*Dimethylaminodihydrocaryophyllene.*—(A) Dry dimethylaminodihydrocaryophyllene methiodide (17 g.), as prepared below and without further purification, was heated in an oil-bath. Smooth decomposition occurred under reduced pressure at 185–200° and the product was allowed to distil. It was dissolved in ether and extracted with dilute sulphuric acid. The base was recovered and gave dimethylaminodihydrocaryophyllene (6.5 g.), b. p. 153–155°/12 mm.,  $n_D^{18}$  1.4953,  $d_4^{18}$  0.9147,  $[\alpha]_D^{18}$  –42.2° (Found: C, 82.3; H, 12.4; N, 5.2.  $C_{17}H_{31}N$  requires C, 81.9; H, 12.5; N, 5.6%). From the ethereal solution a hydrocarbon (2.5 g.) was obtained which on fractionation had b. p. 120–121°/12 mm.,  $n_D^{18}$  1.4990,  $d_4^{18}$  0.9136,  $[\alpha]_D^{18}$  –28.1°, and failed to form a blue nitrosite.

Conversion of the methiodide into the methochloride and subsequent distillation failed to improve the yield of base.

(B; cf. B.P. 581,427) Aminodihydrocaryophyllene (25 c.c.) was mixed with aqueous formaldehyde (40%; 27.5 c.c.), aqueous formic acid (80%; 30 c.c.), and toluene (25 c.c.). The mixture was heated slowly to 45° by which time a vigorous evolution of carbon dioxide had commenced. The reaction was continued with moderate cooling, and gas evolution was completed on the water-bath. The mixture was cooled and washed with an excess of sodium hydroxide solution, and the toluene layer was separated and dried. Fractionation gave dimethylaminodihydrocaryophyllene (21 g.), b. p. 132–134°/2 mm.

*Aminotetrahydrocaryophyllene.*—Aminodihydrocaryophyllene (9.5 g.; b. p. 118–121°/0.7 mm.,  $n_D^{17}$  1.5020; Evans, Ramage, and Simonsen, *loc. cit.*) was hydrogenated in ethanol (300 c.c.) for 8 hr. in the presence of 10% palladium-charcoal (4 g.) at 70°/25 atm. Ethanol was then distilled off and the product fractionated to give aminotetrahydrocaryophyllene (8.3 g.), b. p. 105°/0.5 mm.,  $n_D^{13}$  1.4910,  $d_{20}^{19}$  0.9145,  $[\alpha]_D^{19}$  –13.6° (Found: C, 80.8; H, 12.9. Calc. for  $C_{15}H_{29}N$ : C, 80.6; H, 13.1%).

*Dimethylaminotetrahydrocaryophyllene.*—The above base (10 g.) was converted into dimethylaminotetrahydrocaryophyllene methiodide (15 g.) as described for the dihydro-compound.

Dimethylaminodihydrocaryophyllene (2 g.) in methanol (50 c.c.) was hydrogenated in the presence of 4% palladium-charcoal (1 g.). Dimethylaminotetrahydrocaryophyllene (1.8 g.) had b. p. 120°/1 mm.,  $n_D^{18}$  1.4860,  $d_{20}^{18}$  0.9067,  $[\alpha]_D^{18}$  –7.0°, and was converted into the methiodide.

*Dihydrocaryophyllene-a.*—The methiodide (15 g.) from the preceding experiment was shaken in alcohol (50 c.c.) with an excess of moist silver oxide for 1 hr. After filtration and evaporation the methohydroxide was heated in an oil-bath under reduced pressure and the product allowed to distil whilst the bath-temperature was raised from 145° to 200°. The distillate was washed in ether with dilute hydrochloric acid. Evaporation, followed by fractionation, gave dihydrocaryophyllene-*a* (5.6 g.), b. p. 96°/1.5 mm.,  $n_D^{13}$  1.4850,  $d_{20}^{19}$  0.8843,  $[\alpha]_D^{19}$  –10.2° (Found: C, 87.7; H, 12.4. Calc. for  $C_{15}H_{28}$ : C, 87.3; H, 12.7%). The hydrocarbon corresponded (except in rotation) to the dihydrocaryophyllene obtained from aminotetrahydrocaryophyllene by the action of nitrous acid and dehydration of the resulting alcohol (Evans, Ramage, and Simonsen, *loc. cit.*).

*Oxidation of Dihydrocaryophyllene-a.*—(A) *Permanganate.* The hydrocarbon-*a* (6.5 g.) was oxidised by potassium permanganate (11 g.; 60 mesh) by the procedure for hydrocarbon-*b* below. The neutral product (2.57 g.) on fractionation gave (i) unchanged dihydrocaryophyllene-*a* (0.65 g.), b. p. ca. 90°/1 mm.,  $n_D^{18}$  1.4810, (ii) a ketone (0.72 g.), b. p. 105–120°/1 mm., redistilled b. p. 107–110°/1 mm.,  $n_D^{18}$  1.4810, and (iii) a higher fraction (0.7 g.), b. p. 170°/1 mm., considered to be a keto-aldehyde since hypobromite followed by permanganate gave a dicarboxylic acid  $C_{14}H_{24}O_2$  (dianilide, m. p. 223°).

The sludge gave a gummy acid (4.6 g.) which was treated with sodium bismuthate, yielding a neutral ketone (0.75 g.), b. p. 107–110°/1 mm., which failed to give crystalline derivatives. The recovered acid (3.5 g.) was converted with diazomethane into a mixed keto-ester  $C_{16}H_{28}O_3$  and dicarboxylic ester  $C_{16}H_{26}O_4$ , the latter forming a dianilide, m. p. 223°, and di-*p*-toluidide, m. p. 203°, as below. After hydrolysis and hypobromite treatment of the mixed acids the resulting dicarboxylic acid yielded a *dianilide* (from benzene), m. p. 223° (Found: C, 76.6; H, 8.6.  $C_{28}H_{34}O_2N_2$  required C, 76.8; H, 8.4%), and a *di-p-toluidide* (from aqueous ethanol), m. p. 203° (Found: C, 77.5; H, 9.2.  $C_{28}H_{38}O_2N_2$  requires C, 77.4; H, 8.8%), both colourless needles.

An amorphous *di-p-phenylphenacyl ester* of indefinite m. p. gave the correct analytical results (Found : C, 78.0; H, 7.0.  $C_{42}H_{44}O_8$  requires C, 78.2; H, 6.9%).

(B) *Ozonolysis*. The dihydrocaryophyllene-*a* (4.0 g.) was ozonised in methyl acetate and, when worked up as for the hydrocarbon-*b*, gave an acid (1 g.) and a neutral product (3.5 g.). The former was treated with hypobromite and the resulting dicarboxylic acid  $C_{14}H_{24}O_4$  (0.9 g.) characterised as dianilide, m. p. 223°, and di-*p*-toluidide, m. p. 203°. The neutral product was separated into (i) (1.6 g.), b. p. 110—140°/1 mm., and (ii) (1.5 g.), b. p. 160—190°/1 mm. The former was probably the ketone ( $C_{14}H_{24}O$ ) fraction, giving no crystalline derivatives; the latter was a keto-aldehyde, which by hypobromite and subsequent permanganate oxidation gave the dicarboxylic acid  $C_{14}H_{24}O_4$  (dianilide, m. p. 223°).

*Dimethylaminodihydrocaryophyllene Methiodide*.—(A) Aminodihydrocaryophyllene (10 g.) in methanol (30 c.c.) was gently refluxed on the water-bath with methyl iodide (12.5 g.) whilst methanolic potassium hydroxide (4.7 g. in 50 c.c.) was added during 1 hr. The flask was cooled, more methyl iodide (12.5 g.) added, and the mixture refluxed for a further 3 hr. during the gradual addition of methanolic potassium hydroxide (2.3 g. in 25 c.c.). The alcohol was then distilled off, the residue dissolved in boiling water, and the solution frozen and then allowed to thaw. The methiodide (17 g.), which was a mixture of stereoisomers, was filtered off, washed with water, and dried in a vacuum-desiccator. Further purification was not carried out for the next stage.

(B) Methyl iodide (6 c.c., 10% excess) was slowly run into dimethylaminodihydrocaryophyllene (20 g.) in acetone (100 c.c.) with cooling. The methiodide (22 g.) began to crystallise and a second crop (6 g.) was obtained from the mother-liquors.

*Dihydrocaryophyllene-b*.—Dimethylaminodihydrocaryophyllene methiodide (17 g.) and water (400 c.c.) were added to 5% sodium amalgam (1200 g.; 30 times excess) and heated on a water-bath for 18 hr. whilst carbon dioxide was continuously passed through the solution. The gases issuing from the top of the condenser were bubbled through dilute sulphuric acid to absorb the trimethylamine (picrate, m. p. 215°) produced. After cooling, the product was isolated by extraction with ether and the extracts were washed with dilute acid. From the acid solution dimethylaminodihydrocaryophyllene (1.0 g.), b. p. 138—140°/4 mm.,  $n_D^{15}$  1.4970, was recovered. Fractionation of the ethereal solution gave dihydrocaryophyllene-*b* (7.0 g.), b. p. 110°/7 mm.,  $n_D^{20}$  1.4865,  $d_{24}^{20}$  0.8843,  $[\alpha]_D^{20}$   $-15^\circ$  (Found : C, 87.0; H, 12.5. Calc. for  $C_{15}H_{26}$ : C, 87.3; H, 12.7%).

*Oxidation of Dihydrocaryophyllene-b*.—(A) *Permanganate*. Finely powdered potassium permanganate (20.6 g., 60 mesh) was added during 10 hr., with stirring, to dihydrocaryophyllene-*b* (10 g.) in dry acetone (250 c.c., stable to permanganate) with ice-cooling. After standing overnight the sludge was filtered off, washed with acetone, and suspended in water (300 c.c.) and the manganese dioxide dissolved by an excess of sulphur dioxide. The acidified solution was extracted with ether, and the extract shaken with 20% aqueous sodium hydroxide. The insoluble sodium salt was filtered off and after acidification and extraction with ether yielded a solid product (3.0 g.) which was sublimed and crystallised from cyclohexane, to yield a *hydroxy-acid*, m. p. 143°,  $[\alpha]_D^{17}$   $+35.4^\circ$  (c, 0.792 in MeOH) (Found : C, 70.7; H, 10.0%; equiv., 252.  $C_{15}H_{26}O_3$  requires C, 70.8; H, 10.3%; equiv., 254).

The *methyl ester*, prepared with diazomethane, was purified by sublimation and crystallised from methanol in colourless needles, m. p. 81°, b. p. 118—120°/1 mm. (Found : C, 71.6; H, 10.2.  $C_{16}H_{28}O_3$  requires C, 71.6; H, 10.5%). The *p-phenylphenacyl ester* (Drake and Bronitsky, *J. Amer. Chem. Soc.*, 1930, 52, 3715) crystallised from ethanol in needles, m. p. 148° (Found : C, 77.7; H, 7.7.  $C_{29}H_{36}O_4$  requires C, 77.6; H, 8.1%).

The ethereal solution from which the sodium salts had been removed gave a keto-aldehyde, b. p. ca. 160°/1 mm.,  $n_D^{19}$  1.4982, which reduced Fehling's solution and gave the Adachi colour test (*Analyt. Chem.*, 1951, 23, 1491). Hypobromite treatment, followed by aqueous permanganate oxidation, gave the dicarboxylic acid with a dianilide, m. p. 187°, as described below.

The acetone filtrate, from which the sludge had been filtered, was evaporated and the resulting product (13 g.) on fractionation gave (i) diacetone alcohol (2.0 g.), b. p. 58—59°/10 mm. (Found : C, 60.7; H, 10.4. Calc. for  $C_6H_{12}O_2$ : C, 62.0; H, 10.4%), (ii) unchanged dihydrocaryophyllene (4.1 g.), b. p. 122—123°/10 mm.,  $n_D^{20}$  1.4852, and (iii) a *monoketone* (5 g.), b. p. 133—135°/10 mm.,  $n_D^{20}$  1.4822,  $d_{20}^{20}$  0.9456,  $[\alpha]_D^{20}$   $-33^\circ$  (Found : C, 81.0; H, 11.4.  $C_{14}H_{24}O$  requires C, 80.7; H, 11.6%).

The *semicarbazone* crystallised from ethanol in needles, m. p. 189° (Found : C, 67.7; H, 10.3.  $C_{16}H_{27}ON_3$  requires C, 67.9; H, 10.3%), and the 4-*phenylsemicarbazone*, m. p. 183°, crystallised similarly (Found : C, 73.8; H, 9.1.  $C_{21}H_{31}ON_3$  requires C, 73.9; H, 9.2%). The 2 : 4-*dinitro-*

*phenylhydrazone* crystallised from ethanol in clusters of long orange needles, m. p. 147° (Found : C, 62.3; H, 7.4.  $C_{20}H_{28}O_4N_4$  requires C, 61.8; H, 7.3%). The ketone and the derivatives were identical with those reported in the previous paper.

The above hydroxy-acid (0.4 g.; m. p. 143°), sodium bismuthate (0.38 g.), and glacial acetic acid (5 c.c.) were shaken for 5 hr., by which time the orange colour had disappeared. After removal of the acetic acid under reduced pressure the ketone  $C_{14}H_{24}O$  (0.2 g.) was isolated by ether-extraction; the 4-phenylsemicarbazone, m. p. 183° (Found : C, 74.1; H, 9.5%), and 2:4-dinitrophenylhydrazone, m. p. 147° (Found : C, 62.0; H, 7.6%), were identical with the derivatives recorded above.

From the soluble sodium salt accompanying the hydroxy-acid, a keto-acid was recovered and purified by fractionation as its *methyl ester* (0.4 g.), b. p. 125°/0.1 mm. (Found : C, 70.7; H, 10.7.  $C_{16}H_{28}O_3$  requires C, 71.6; H, 10.5%). This keto-acid was more readily available from the following procedure.

(B) *Ozonolysis*. Dihydrocaryophyllene-*b* (10 g.) was ozonised to completion in methyl acetate, and the ozonide decomposed by boiling water after removal of the solvent. The product after treatment for several days with hydrogen peroxide (5 c.c.; 20-vol.) was separated into the above ketone  $C_{14}H_{24}O$  (9.0 g.) and an acid (1.5 g.) which was purified through its methyl ester, b. p. 125°/0.1 mm.,  $n_D^{18}$  1.4520. The keto-ester was hydrolysed and treated with sodium hypobromite, and the resulting dicarboxylic acid recovered. The dianilide, crystallised from aqueous ethanol, had m. p. 187° (Found : C, 76.8; H, 8.5. Calc. for  $C_{26}H_{34}O_2N_2$  : C, 76.8; H, 8.4%).

*Dihydroisocaryophyllene Oxides*.—(A) *isoCaryophyllene oxide-a* (5 g.) was hydrogenated in acetone (60 c.c.) at atmospheric pressure in the presence of platinum. Removal of the catalyst and solvent followed by fractionation of the product gave *dihydroisocaryophyllene oxide-a*, b. p. 140—145°/12 mm.,  $n_D^{17}$  1.4810,  $[\alpha]_D^{20}$   $-29.6^\circ$  (*c*, 2.210 in MeOH), which crystallised from methanol in plates, m. p. 50—51° (Found : C, 80.7; H, 11.5.  $C_{15}H_{26}O$  requires C, 81.0; H, 11.8%).

(B) Similarly *oxide-b* gave *dihydroisocaryophyllene oxide-b* as an oil, b. p. 138°/8 mm.,  $n_D^{17}$  1.4826,  $[\alpha]_D^{19}$   $+10.2^\circ$  (*c*, 4.100 in MeOH) (Found : C, 81.7; H, 11.8%).

*Dihydrocaryophyllene Oxide* (Treibs, *loc. cit.*).—Caryophyllene oxide (5 g.) gave dihydrocaryophyllene oxide (4.7 g.), b. p. 139—140°/12 mm., m. p. 67°.

In connection with the work described in this and the preceding paper, the authors thank Imperial Chemical Industries Limited for chemicals, and the Huddersfield Education Authority for the award of the Armytage and British Dyes Research Scholarships to B. W. and R. W. respectively.