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CYCLIZATION OF NEROL AND LINALOOL ON SOLVOLYSIS OF THEIR PHOSPHATE ESTERS

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Abstract—The cyclization of phosphate esters of Nerol and Linalool occurs via an anchimerically assisted nucleophilic attack of the 2,3-double bond on C-8 of the terpene. The non-classical cation (Fig. 1, II) thus formed can either add water to give α-terpineol or rearrange to the classical ion (Fig. 1, III), which gives α-terpineol and elimination products. The anchimeric assistance is shown by rate studies. Internal return in neryl carbonium ions can be excluded by ^{18}O-labelling experiments. Studies on sesquiterpene solvolysis give additional proof of the mechanism.

AS DESCRIBED in a previous communication[1] cyclization of neryl and linaloyl phosphate and pyrophosphate takes place on hydrolysis to give monocyclic terpenes. In this paper the mechanism of this cyclization is studied. The results reported here are primarily valid for the phosphate esters, but it can be expected that the situation with pyrophosphates is basically not very different.

Cyclization of acyclic to monocyclic monoterpenes is long known. Zeitschel[2] proved *cis*-configuration for nerol by showing that it cyclizes nine times faster to terpin hydrate via α-terpineol in dilute sulphuric acid than the geraniol which is of *trans*-configuration.[3] Earlier Stephan[4] had found that levoratatory linalool and linaloyl acetate can be transformed into dextrorotatory α-terpinyl acetate in glacial acetic acid–sulphuric acid. Several explanations[5] of the mechanism of this reaction

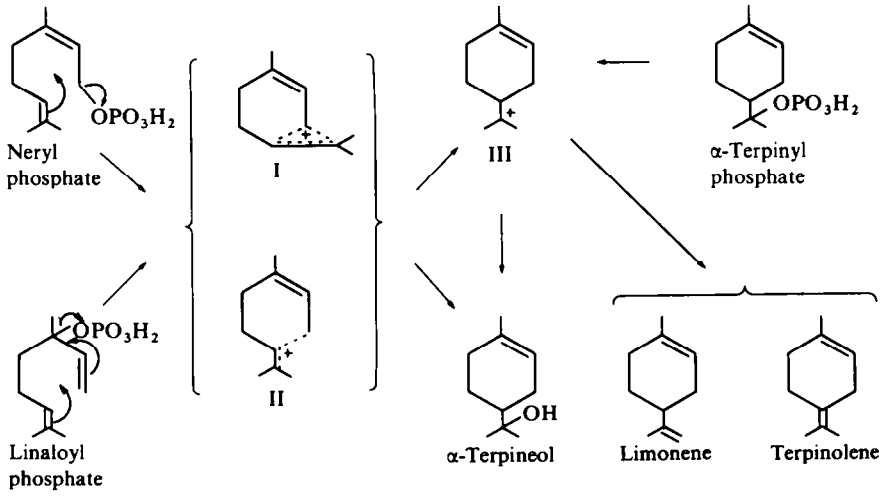

FIG. 1 Pathways of cyclization in solvolysis of neryl, linaloyl and α-terpinyl phosphate.

were unsatisfactory since the absolute configuration of linalool was not known. Only the recent determination of (−)-linalool to be the R-compound[6] opens up possible explanations. We propose that the cyclization of neryl and linaloyl phosphate occurs by nucleophilic attack of the 2,3-double bond on the C-8 atom and elimination of the phosphate residue (Fig. 1). Thus in the case of neryl phosphate an internal S_N2-reaction and in the case of linaloyl phosphate an internal S_N2'-reaction occurs. Anchimeric cyclizations of the kind described here have found some interest recently since these cyclizations occur under very mild and kinetically controlled conditions, and, therefore, can serve as models for biogenetic cyclizations.[7] The following observations are in favour of an anchimeric cyclization.

The *cyclization* of neryl and linaloyl phosphate cannot go through the neryl cation[1] as a common intermediate since the ratio of cyclic versus acyclic compounds is different in both cases. (Table 1, second row). The same would apply when

TABLE 1. PRODUCT RATIOS IN SOLVOLYSIS OF MONOTERPENE PHOSPHATES, CALCULATED FROM THE VALUES GIVEN[1]

Phosphate	Primary/tertiary Acyclic alcohols	Cyclic/acyclic Alcoh. + hydrocarb.	Cyclic alcohols/ Cyclic hydrocarbons
Geranyl	0·25	—	—
Neryl	0·24	1·9	15·1
Linaloyl	0·24	0·2; 0·9*	16·2
α-Terpinyl	—	—	4·4

* Calculated for the neryl cation, supposing neryl cation/geranyl cation = nerol/geraniol (see also Ref. 39).

assuming that with linaloyl phosphate the cyclic products are formed solely from neryl cation and not from the geranyl cation. The neryl cation, however, is a common intermediate in the formation of the *acyclic* compounds because the relation of primary and tertiary alcohols is almost equal in both cases (Table 1, first row), the product spread is very small (about 0·5%). Moreover, the linalool formed from the levorotatory linaloyl phosphate is racemic; the α-terpineol, in contrast, is still 40% dextrorotatory. Since the absolute configuration of (+)-terpineol[8] and (−)-linalool[6] is known, it is obvious that the cyclization from linalool phosphate obeys the known stereochemistry of S_N2'-reactions in allylic compounds:[9] Entering of the nucleophile and outgoing of the leaving group occur on the same side of the molecular plane (Fig. 2).

With neryl phosphate this mechanism also follows from kinetic measurements. Assuming that the cyclization as well as the non-anchimerically assisted hydrolysis are side-reactions of the same order, the following equation may be written:[10]

$$\frac{k_{NP} - f_i \cdot k_{HNP}}{f_i \cdot k_{HNP}} = \frac{\text{cycles}}{\text{acycles}}^*$$

* k_{NP} = hydrolysis constant of neryl phosphate; k_{HNP} = hydrolysis constant of 2,3-dihydroneryl phosphate; f_i, the retarding inductive effect, follows from the ratio of the hydrolysis constants of geranyl phosphate (k_{GP}) versus 2,3-dihydrogeranyl phosphate (k_{HGP}):

$$f_i = k_{GP}/k_{HGP}$$

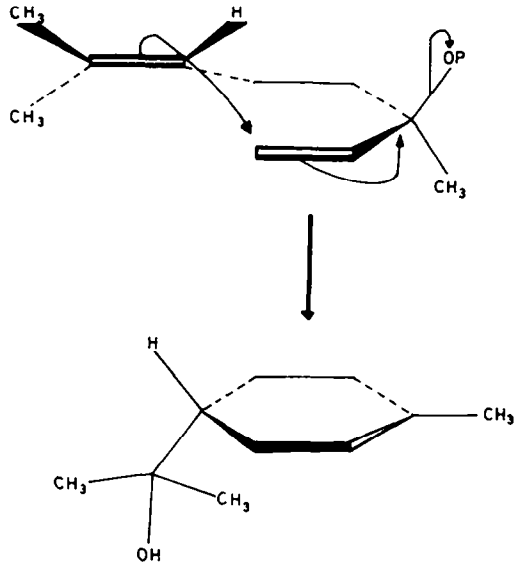

FIG. 2 Stereochemical course of the reaction of (−)-(R)-linaloyl phosphate to give (+)-(R)-α-terpineol.

If the molecular weight of cyclic and acyclic compounds is equal an expression for the anchimeric acceleration may be written as follows:

$$\frac{k_{NP}}{f_i \cdot k_{HNP}} = \frac{\%\ \text{cycles}}{\%\ \text{acycles}} + 1$$

The rates of hydrolysis at pH 1·2 and 25° were measured and are given in Table 2. From these values the inductive factor f_i is found to be 0·5 and the anchimeric assistance $k_{NP}/f_i \cdot k_{HNP} = 2{\cdot}5$. From this a ratio cyclic/acyclic compounds of 1·5 is calculated which corresponds to 60% cyclic products; 66% cyclic products were

TABLE 2. HYDROLYSIS CONSTANTS (MIN^{-1}) OF SOME PHOSPHATE ESTERS AT pH 1·2 and 25°

2,3-Dihydro-neryl phosphate (HNP)	Neryl phosphate (NP)	2,3-Dihydro-geranyl phosphate (HGP)	Geranyl phosphate (GP)	Geranyl phosphate (GP) lit[21]
$k \times 10^2$: 6·4	8·1	9·2	4·6	4·2

found.[1] A further indication for the anchimeric cyclization is the fact that in both cases the character of the leaving group influences the degree of cyclization: from the neryl- as well as in the linaloyl *pyro*phosphate more α-terpineol is formed than with the respective phosphates.[1]

In contrast to the solvolysis of linaloyl *p*-nitrobenzoate in 70% aqueous acetone[12] in which a considerable portion of internal return to geranyl, neryl, and α-terpinyl *p*-nitrobenzoate occurs, internal ion pairs do not play a great role in our experiments. Thus on hydrolysis of linaloyl phosphate no phosphates of geraniol, nerol, and

α-terpineol could be detected in spite of the fact that the latter phosphates hydrolyse about ten times slower. Also during hydrolysis of neryl phosphate no α-terpinyl phosphate could be found. On hydrolysis of ^{18}O-labelled neryl phosphate $C_{10}H_{17}\text{-}^{16}OP^{18}O_3H_2$ no significant distribution of the isotopes occurred. The labelled neryl phosphate was prepared from non-labelled nerol and labelled phosphorous acid according to Kirby.[13] The hydrolysis was interrupted after it had proceeded to about 50% hydrolysis and the isolated phosphate ester was split enzymatically by fission of the P–O-bound[14] with bovine alcaline phosphatase. The resulting nerol had an ^{18}O-content which was lower than 1% of the phosphorous acid used.

The cyclization of (−)-linalool in acetic acid-sulphuric acid[4] and aqueous sulphuric acid[2,15] to give (+)-α-terpinyl acetate and (+)-α-terpineol respectively should also proceed by an internal S_N2'-mechanism, since in these systems no ion pairs are possible by definition.[16] The intramolecular attack of a double bond on an allylic system has only been studied in a few examples. Recently Johnson *et al.*[17] reported the formolytic cyclization of (3-butenyl) cyclohexen-2-oles to give derivatives of *cis*-octalol which most likely occur according to an A_E-mechanism by addition of the allyl cation to the butenyl double bond. The same should be the case in the cyclization of zingiberene to give isozingiberene[18] or of farnesene to give bisabolene[19] and of myrcene to give α-terpineol.[20]

Fig. 1 shows the possible intermediates in the cyclization of neryl and linaloyl phosphate.*

The classical terpinyl cation III cannot be the only intermediate of this cyclization since the relation of substitution and elimination in this case is quite different from the one in the cyclization of α-terpineol phosphate (Table 1, fourth row). The hydrolysis of the latter must go through the classical ion III.

From the acyclic phosphates smaller amounts of cyclic hydrocarbons are formed than from the cyclic phosphates. This is in agreement with an observation by Bartlett[7a,21] that on acetolysis of 5-hexenyl *p*-nitrobenzenesulfonate much less cyclohexene is formed than on acetolysis of cyclohexyl *p*-nitrobenzenesulfonate. Bartlett proposes a bridged ion which can expel a proton only with difficulty. A differentiation of the various species I, II and III shown in Fig. 1 is possible in principle by looking at the addition of solvent to the particular species. The attack of water should be stereospecific in the symmetrically bridged cyclopropane-like cation I. Also in the synchroneous cyclization and addition of water stereospecificity should be observed. To the non-symmetric species II water should add stereoselectively whereas the attack on the classical terpinyl cation III should be non-stereospecific. Such observations are not possible with monoterpenes since the double bond which is involved in this reaction is substituted symmetrically. Only from non-symmetrically substituted double bond two asymmetric C-atoms are formed which can give rise to the formation of diastereomeres. Therefore, cyclization of *cis*- and *trans*-nerolidyl phosphates as well as of *cis-trans*-farnesyl phosphate to give bisabolol[22] was studied (Fig. 3). The trimethylsilylether of bisabolol can be separated into the diastereomeres by VPC. The relation of the diastereomeres is shown in Table 3.

* We are grateful to Prof. E. J. Corey for the suggestion to consider the non-classical ion II also.

TABLE 3

Educt	% *threo*-Bisabolol	% *erythro*-Bisabolol
cis-trans-Farnesyl phosphate	39	61
trans-Nerolidyl phosphate	45	55
cis-Nerolidyl phosphate	51	49
Bisabolol, synthetical	51	49

Calculated: peak height × half-width.

From this it is seen that the attack on the "*trans*"-bisabolyl cation is stereoselective.

Nothing is known about the diastereomeric bisabolols. We assume that the preferred diastereomer is formed by *trans*-addition on to the middle double bond and, therefore, is the *erythro-form.** Addition of water to the "*cis*"-bisabolyl cation is non-stereospecific. When transferring these findings with the sesquiterpenes to the monoterpene series which should be allowed with restrictions† one comes to the following conclusions:

The intermediate in the cyclization of monoterpenes is either the symmetrical non-

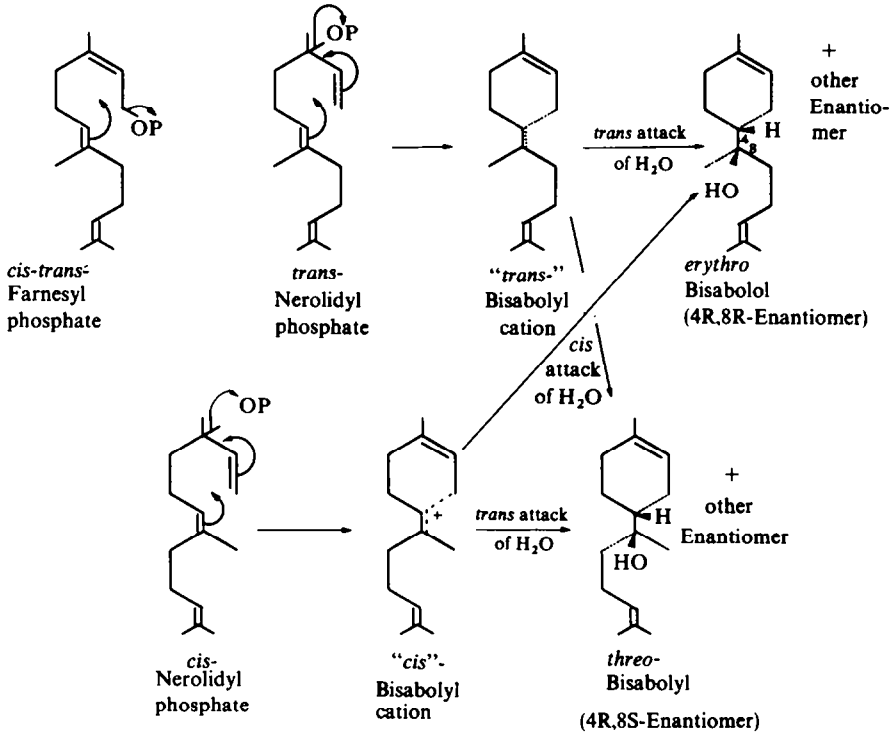

FIG. 3 Stereochemistry of cyclization of farnesyl- and nerolidyl-phosphates.

* We call this diastereomer "*erythro*" because its asymmetric C-atom possesses the same chirality like erythrose, namely (R,R) for the one and (S,S) for the other enantiomer.

† The composition of the products of hydrolysis of the sesquiterpenyl phosphates is different from the composition in the monoterpene reactions. Preliminary measurements showed substantially more hydrocarbons (20% from farnesyl phosphate).

classical cation I (Fig. 1) which rearranges partly into the classical terpinyl cation III. The other possibility is the intermediary non-symmetric, non-classical cation II (Fig. 1) which can also rearrange into III. This transformation is necessary for the formation of hydrocarbons; especially in the case of terpinolene this compound cannot be formed from a non-classical ion for steric reasons. We are inclined to prefer II as an intermediate, mainly because of steric grounds. Dreiding models of neryl phosphate show that in the transition state on *symmetrical* attack of C-8 on the 2,3-double bond H-5 and H-6 as well as H-7 and the phosphate residue occupy eclipsed conformations. Such transition states are unfavourable for cyclization.[23] When, however, C-8 attacks the double bond at C-3 *unsymmetrically* an all-staggered conformation is established in the neryl and linaloyl phosphate case. The unsymmetrical attack which in this case, therefore, is favoured energetically in comparison with the symmetrical attack leads to the unsymmetrical cation II. The picture in Fig. 1 is an extreme case which shall only indicate that the orbital at C-8 overlaps more with the orbital at C-3 than with the orbital at C-2: II has more the character of a 6- than of a 7-membered ring. 7-membered ring cations seem to be not very favoured, even in the tertiary case because the solvolysis of 6-methyl-6-heptenyl-nitrobenzenesulphonate yields only traces of 1-methylcycloheptanol and no dimethylcyclohexanol.[24]

The non-specificity of the addition of water to the "*cis*"-bisabolyl cation does not necessarily rule out for a formulation analogous to II, since steric hinderance between isohexenyl group and saturated part of the cyclohexene-like cation most likely bring about a twist of the molecule around the axis C-6–C-7 and, therefore, would make the attack of water from both sides of the molecule equivalent.

EXPERIMENTAL

M.ps and b.ps are not corrected. An Autoprep A 700 (Wilkens Instrument and Research Inc.) was used for preparative VPC and a fractometer 116 E (Bodenseewerk Perkin-Elmer) for analytical VPC. Optical rotations were measured with a polarimeter 141 (Bodenseewerk Perkin-Elmer).

O^{18}-determinations were carried out with a mass spectrometer CH4 (Atlas).

Starting materials. Commercial nerolidol (Roth) was almost pure *trans*-isomer, commercial farnesol (Fluka) consisted of *cis-trans*- and *trans-trans* isomers in the approximate ratio of 2:3.

Nerylacetone. Nerylacetone was prepared in analogy to the procedure of Mondon[25] for geranylacetone. b.p.$_{15}$ 125–130°; n_D^{20} 1·4718; I^A_{190} 1377; I^P_{190} 1835. *Content.* 80%, 10% geranylacetone (I^A_{190} 1397; I^P_{190} 1860); the rest consists most likely of neryl acetoacetic acid ester. The VPC peaks of the main and by-product were identical with those of a mixture of geranyl- and nerylacetone prepared according to Carrol.[26]

cis-*Nerolidol.* This compound was synthesized[27] from nerylacetone and vinylmagnesiumbromide. b.p.$_{12}$ 144–146°; n_D^{20} 1·4810; I^A_{190} 1495; I^P_{190} 1985. *Content.* 85%, 10% *trans*-nerolidol (I^A_{190} 1530; I^P_{190} 2022). The IR spectrum of a sample which was extensively purified by VPC showed only one single peak at 833 cm^{-1}, as described,[33] whereas the *trans* compound showed a peak with two shoulders at this position.

4-*methyltetrahydroacetophenone.* This compound was synthesized from isoprene and methylvinylketone according to Alder and Vogt.[28] It contained about 30% of the 3-methyl-isomer. b.p.$_{15}$ 83–85°, semicarbazone m.p. 150°.

Bisabolol. Bisabolol was synthesized from methyltetrahydroacetophenone and the Grignard compound of 4-methyl-1-bromo-pentene-3 (preparation see[29]) according to Ruzicka and Liguori.[30] Due to the contamination of the ketone it contained about 30% of "meta"-bisabolol. This compound was not purified any further. I^A_{190} 1688; I^P_{190} 2196; "meta"-bisabolol: I^A_{190} 1671; I^P_{190} 2181. The IR spectrum of a sample which was extensively purified by VPC was identical with the one published.[31]

Attempts to separate bisabolol into the diastereomers by VPC on apiezon L, polyethyleneglycol20,000 and polyphenylether OS 124 were unsuccessful.

Bisabolyl-trimethylsilyl-ether. The crude bisabolol was heated for 1 hr to 160° with an excess of trimethylsilylacetamide (preparation 36).[32] After cooling pentate was added, the precipitated acetamide centrifuged off, the supernatant evaporated and analysed by VPC. On a Golay column (50 m steel) covered with half of the usual amount (4% impregnation solution[1]) of polyphenyl ether OS 124 at 180° and 1 atmosphere, the separation of the diastereoisomerides was best. On polyethylene glycol 20,000 the separation was not as clean, on apiezon L it was satisfactory but here *threo*-silylether and unreacted bisabolol could possibly interfere. *threo*-Silylether: I^{OS}_{180} 1805; $I^{\wedge}_{190}$ 1702; I^{P}_{190} 1871; *erythro*-silylether I^{OS}_{180} 1811; $I^{\wedge}_{190}$ 1709; I^{P}_{190} 1878.

Mixture of cis-trans *and* trans-trans *farnesyl phosphate.* Farnesyl phosphate was prepared[34], the modified procedure[1] did not yield the desired products. R_f-value 0·76.*

cis- *and* trans-*Nerolidyl phosphate.* Preparation of the isomeric nerolidyl phosphates was carried out according to the modified procedure.[1] R_f-value 0·71.*

Acid hydrolysis of the sesquiterpenyl phosphates. The acid hydrolysis was carried out in accordance with monoterpenyl phosphates[1] scaled up 5- to 10-fold. The dried pentene layer was concentrated to about 1 ml and injected into the preparative VPC. *Column.* 25% carbowax 20 M on chromosorb W, silanized, 60–80 mesh; *temperature*: 230°; flow rate 120 ml/min. The peak of bisabolol (retention time about 50 min) was collected in a trap cooled with dry ice-acetone, transformed into the trimethylsilyl ether, as described above, and analysed for its ratio of diastereoisomerides by capillary gas chromatography.

Determination of the rate of hydrolysis of geranyl- and neryl phosphate and its 2,3-*dihydro derivatives*

The rate of hydrolysis of these compounds[1, 35] was determined in close analogy to the method of Eggerer (hydrolysis[11]) and Chen *et al.* (phosphate determination)[36]: 18·7 mg terpenyl phosphate (cyclohexylammoniumsalt) was dissolved in 10 ml water and kept at 25°.

At 0 min, 10 ml of 0·1N glycin-buffer pH 1 was added, the final pH of the mixture was 1·2.

After 6, 9, 12, 15, and 18 min and after a short heating period (time ∞) samples of 5 ml each were taken and pipetted into 1 ml Br_2 soln. To it 5 ml of molybdate reagent was added and kept at 37° for 2 hr. After addition of water up to 25 ml the extinction at 820 mμ was measured.

Bromine solution: 12 g of NaBr and 0·52 ml Br_2 dissolved in 100 g abs MeOH. Molybdate reagent: 30 ml 2N H_2SO_4 + 10 ml 2·5% aqueous ammoniummolybdate soln + 13 ml 10% aqueous ascorbic acid soln.

Hydrolysis of optically active linaloyl phosphate

Compound	Source	Concentration in % (MeOH)	$[\alpha]_D^{20}$
Linalool	starting material	0·5	− 21·5
Linalool	reference[37]	undiluted	− 21·6
Linalool	enzym. cleavage	0·23	− 20·9
Linalool	acid hydrolysis	1·27	± 0
α-Terpineol	acid hydrolysis	0·14	+ 39·7
α-Terpineol	acid hydrolysis	0·26	+ 42·6
α-Terpineol	reference[38]	5 (EtOH)	+ 100·5

(a) *Enzymatic cleavage.* 250 mg of (−)-linaloyl phosphate, 50 mg of alkaline phosphatase (Worthington), and 3 drops of 1M $MgCl_2$-soln were incubated in 25 ml buffer pH 9 for 3 days at 25°. After 24 hr, again the same amount of enzyme was added. The cleavage was not quite complete. The cleaved linalool was extracted with pentane, the pentane layer was thoroughly dried with Na_2SO_4 and evaporated in a vessel of known weight. The residue was dissolved in MeOH and the rotation measured.

(b) *Acid hydrolysis.* 500 mg of (−)-linaloyl phosphate was hydrolysed as described in.[1] The hydrolysis mixture was separated by preparative VPC. *Column*: 25% polyethylene glycol 20,000 on chromosorb W, silanized 60–80 mesh, temperature: 180°; flow rate 120 ml/min. Linalool and α-terpineol were collected in traps of known weight, dissolved in MeOH and the rotation measured.

* Solvent: isopropanol : conc. NH_3 : water = 7 : 1 : 2 (cf. Refs 1, 39).

Experiments for the distribution of isotopes

^{18}O *Phosphorous acid.* This compound was synthesized according to a procedure in Inorganic Synthesis[39] from PCl_3 and 2% $H_2{}^{18}O$ (Fluka).

Neryl ^{18}O-phosphate. The labelled neryl phosphate was prepared in accordance with the procedure of Kirby:[13]

0·8 g of ^{18}O-phosphorous acid and 5·0 ml of Et_3N were dissolved in 40 ml nerol, cooled with ice water, and 3·8 g finely powdered I_2 was added in small portions. After stirring for about ½ hr it was diluted with 150 ml acetone and gaseous NH_3 introduced. The ppt was filtered off, washed with acetone and recristallized from cyclohexylamine containing water to expel NH_3. The cyclohexylammoniumsalt of the labelled neryl phosphate was pure by paper-chromatography, yield: 1·4 g (32% based on H_3PO_3).

Enzymatic cleavage of neryl ^{18}O-phosphate. 300 mg of neryl phosphate, 50 mg of alkaline phosphatase (Worthington), and 3 drops of a 1M $MgCl_2$ soln were dissolved in 30 ml borate buffer pH 9 and incubated over night at 25°. The cleavage was quantitative. The cleaved nerol was extracted with pentane, the pentane layer was thoroughly dried with Na_2SO_4 and evaporated. The residue, pure nerol by VPC, was transformed into CO_2 for the determination of isotopes (see below).

Partial acid hydrolysis of neryl ^{18}O-phosphate. 900 mg of neryl phosphate was dissolved in 50 ml water and treated with 100 ml 1N H_2SO_4 at room temp. After 4 min, the hydrolysis was stopped by pouring the soln into 50 ml conc NH_4OH. (Paper chromatography indicated that the hydrolysis had proceeded to about 50%). After evaporation to dryness on the rotary evaporator the residue was extracted with boiling MeOH to separate the unreacted neryl phosphate from ammonium sulphate and -phosphate. The methanolic soln was evaporated to dryness *in vacuo*, the residue washed with pentane and cleaved enzymatically as described above.

Labelled ^{18}O-KH_2PO_4. For the determination if isotopes the phosphorous acid had to be transformed into KH_2PO_4: 0·5 g of labelled phosphorous acid was dissolved in 5 ml water and treated with about 50 ml saturated Br_2 water. After 10 min, the excess Br_2 was destroyed with isoprene, the soln brought to pH 4·4 with 10% KOH aq and treated with a threefold volume of EtOH. The ppt was filtered off, washed with EtOH and dried over P_2O_5. No bromide could be detected with $AgNO_3$. The exchange of isotopes with $H_2{}^{16}O$ in acid medium can be neglected:

$$H_3PO_3 : t_{\frac{1}{2}} = 6{\cdot}5 \text{ hr } (63°); H_3PO_4 : t_{\frac{1}{2}} = 70 \text{ hr } (100°)^{40}$$

Transformation into $^{18}CO_2$. The ^{18}O in KH_2PO_4 was transformed into CO_2 according to the method of Boyer.[45] This method which is also suited for water, was modified for the transformation of oxygen from nerol into CO_2: instead of water nerol and a trace of I_2 as a catalyst for dehydration was heated for 4 hr to 260° together with guanidire hydrochlorid in a sealed tube. The complete dehydration of nerol could be shown by VPC. During transfer of CO_2 into the storage vessel of the mass spectrometer the terpene hydrocarbons were trapped into a U-tube cooled with aceton-dry ice.

Determination of ^{18}O-content. The composition of isotopes in CO_2 was determined by mass spectrometry. The ^{18}O content was calculated according to the formula below:[41]

$$\text{atom-\% } {}^{18}O = \frac{100 \cdot R}{2 + R} \qquad R = \frac{\text{abundance mass 46}}{\text{abundance mass 44}}$$

Sample	100 · R	atom-% ^{18}O
Nerol, natural	0·4059	0·203
	0·4061	0·203
Nerol from nerylphosphate, enzymatically cleaved	0·4012	0·200
Nerol from neryl phosphate, partially hydrolysed,	0·4218	0·210
reisolated and enzymatically cleaved	0·4208	0·210
KH_2PO_4 from H_3PO_3	2·9313	1·444
	2·9257	1·442
H_3PO_3, calculated		1·92

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* The "cyclization" of geraniol is preceded by an allylic rearrangement to form linalool which then undergoes cyclization. This can been seen when following the course of the reactions of geraniol, nerol, and linalool in dilute H_2SO_4.[3]

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