*Tetrahedron* Vol 32, pp 1423 to 1425 Pergamon Press 1976. Printed in Great Britain

# STUDIES IN SESQUITERPENES—L†‡

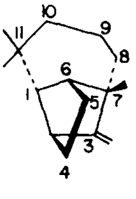
## 3-HYDROXYLONGIFOLALDEHYDE, THE ELUSIVE INTERMEDIATE IN THE ABNORMAL PERBENZOIC ACID OXIDATION OF LONGIFOLENE‡

A. P. JOSHI, U. R. NAYAK and SUKH DEV*§
National Chemical Laboratory, Poona, India

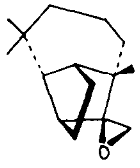
(*Received UK* 15 *January* 1976; *Accepted for publication* 9 *February* 1976)

**Abstract**—The isolation and stereochemistry of 3-hydroxylongifolaldehyde (**4**), the missing key-compound in the earlier proposed mechanism for the abnormal perbenzoic acid oxidation of longifolene is described. Rearrangement of hydroxyaldehyde (**4**) to hydroxyketone (**6**) during exposure to LAH is reported.

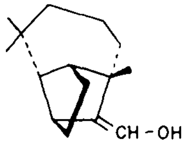
Reaction of a $CHCl_3$ soln of perbenzoic acid (PBA) with longifolene (**1**) is abnormal[1,2] in that the product is not the expected epoxide (**2**), but almost 2 moles of the peracid are rapidly consumed resulting in a complex mixture of products in which the norketone (longicamphenilone, **5**) and the hydroxy ketone (**6**)[2,3] predominate. These results are rationalized[2] in terms of isomerization of the initially-formed epoxide to the enol (**3**), which rapidly reacts further with the peracid to generate the products observed; the facile isomerization of the epoxide to the enol was attributed to the relief of steric compression accompanying the change in the hybridization at $C_3$ from $sp^3$ to $sp^2$. 3-Hydroxylongifolaldehyde (**4**) was implicated as the intermediate in going from the enol to the products **5**, **6**. It had not been possible at that time to isolate or even get evidence for the presence of the hydroxyaldehyde. We now describe conditions of reaction, which has permitted us to isolate this elusive intermediate.¶



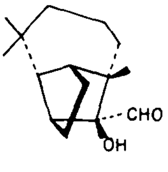
**1**



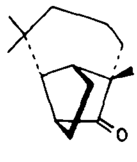
**2**



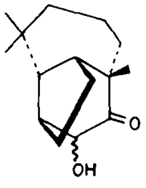
**3**



**4**



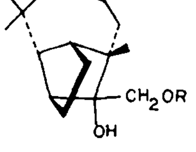
**5**



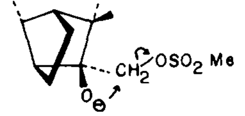
**6**

It has been found now that if the peracid oxidation (two mole equiv) is carried out in a mixture of carefully purified $CHCl_3$ and ethanol (10%),[ǁ] one can isolate after 48 hr at ~5°, a crystalline compound (yield ~55%) analysing for $C_{15}H_{24}O_2$ ($M^+$, $m/e$ 236). From its spectral characteristics, it became clear, at once, that the compound is the long-sought-for intermediate, 3-hydroxylongifolaldehyde (**4**): OH (IR: 3400, 1040 cm$^{-1}$), $\overset{|}{\underset{|}{-C-}}CHO$ (PMR: 1H, s, 11.13 ppm; IR: 2670, 1710 cm$^{-1}$). The compound readily formed a semicarbazone (m.p. 210°) and a 2,4-dinitrophenylhydrazone (m.p. 200–201°). Structure **4** (stereochemistry not implied) was confirmed, when periodic acid in aq. MeOH cleaved it to the expected longicamphenilone (**5**).

That the hydroxyaldehyde has the stereochemistry depicted in **4** was established by correlating it with longifolene epoxide (**2**) which has a well-secured[2,4] stereochemistry. Hydroxyaldehyde **4** on exposure to LAH gave as one of the products (*vide infra*) the expected diol (**7**), which on treatment with mesyl chloride and pyridine gave the required mesylate (**8**). It was expected (cf. **9**) that this mesylate will collapse to the epoxide on exposure to a mild base. However, under the conditions investigated (10% $NaHCO_3$ aq; passing its benzene soln through a column of basic alumina, Brockmann activity II) further isomerization[4] of the epoxide to longifolaldehyde (epimeric mixture) took place. The required transformation could ultimately be achieved by treating the mesylate with LAH in refluxing ether; evidently alkoxide displacement (**9**) of the mesylate occurs under the essentially neutral conditions to produce epoxide **2**, which is sterically shielded from an hydride attack.[6] The product was completely identical (m.p., m.m.p., IR, PMR) with longifolene epoxide (**2**), thus securing the stereochemistry of hydroxyaldehyde as depicted in **4**. It may be pointed out that this $C_3$-configuration was expected since attack of



**7**: R = H
**8**: R = $SO_2CH_3$



**9**

---

†Communication No. 1985, National Chemical Laboratory, Poona, India.

‡Part XLIX. *Tetrahedron* **29**, 985 (1973).

§Present address: Malti-Chem. Research Centre, Nandesari, Vadodara, India.

¶Presented at the Eighth I.U.P.A.C. Symposium on the Chemistry of Natural Products, New Delhi (1972). Abstract Book, p. C-53.

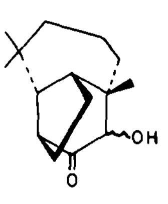
[ǁ] Primarily added to inhibit decomposition of $CHCl_3$ during the course of the peracid reaction.

the peracid on the enol 3 should preferentially occur from the more accessible *endo*-face.[2,5]

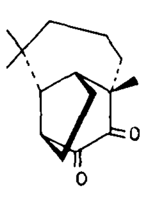
As expected, compound **4**, readily generates longicamphenilone (**5**), the major "abnormal" product of PBA oxidation, under conditions, which may be expected to prevail during the PBA oxidation. Thus, further oxidation of **4** with PBA results in Baeyer–Villiger oxidation to furnish, after work-up, the norketone (**5**) in 85–90% yield. Indeed longicamphenilone (**5**) can now be readily prepared in 80–85% yield (based on longifolene) by subjecting longifolene to oxidation with three molar equivalents of PBA in $CHCl_3$—10% EtOH.

On the other hand, when exposed to an acidic medium (1% *p*-toluenesulfonic acid in $CHCl_3$, 25°, 30 min), the hydroxyaldehyde readily rearranged to ketol **10** rather than to the isomeric ketol **6**, isolated earlier by Lhomme and Ourisson,[3] as one of the oxidation products of longifolene with monoperphthalic acid.† The two ketols are readily distinguishable by PMR: C$\underline{H}$OH (**6**: d, 4.47 ppm, J = 4 Hz; **10**, s, 3.82 ppm). These ketols are quite labile and undergo rapid air oxidation to longidione (**11**) and hence, are best isolated as the corresponding acetates. Though, ready isomerisation of the hydroxyaldehyde was anticipated,[2] it is difficult to rationalise this difference in product development in the two cases.

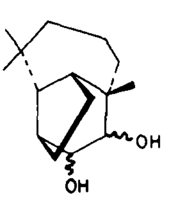
When refluxed with cupric acetate in acetic acid, the hydroxyaldehyde smoothly passed over to longidione (**11**).



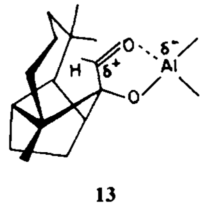
**10**



**11**



**12**



**13**

As already stated, reaction of the hydroxyaldehyde with LAH was carried out to get the required glycol **7**. However, this reaction gave the expected glycol in only ~50% yield, other products being ketol **6** (~40%) and rearranged glycol **12**. Conceivably, this rearrangement can occur through a complex such as **13**, in which the aldehydic carbon is well-shielded; Lewis acid character of LAH has been recognised as one of its characteristics responsible for molecular rearrangements observed during LAH reductions.[7]

## EXPERIMENTAL

All m.ps and b.ps are uncorrected. Light petroleum refers to the fraction b.p. 60–70°. All solvent extracts were finally washed with brine and dried over $Na_2SO_4$. Optical rotations were measured in $CHCl_3$.

TLC was carried out on silica gel layers (0.3 mm) containing 15% gypsum.

The following instruments were used for spectral data: Perkin-Elmer Infracord, model 137-E (IR); Varian Associates A-60 spectrometer (PMR; TMS as internal standard); CEC mass spectrometer, model 21-110B (Mass; 70 eV, direct inlet system). While summarising mass spectral data, besides the molecular ion, ten most abundant ions (above *m/e* 50) are given with their relative intensities.

### 3-*Hydroxylongifolaldehyde* (4)

To a soln of longifolene (40.8 g, 0.2 mole) in freshly purified[8] $CHCl_3$ (100 ml), cooled to −10°, was introduced a freshly prepared cold soln (~0°) of PBA (55.2 g, 0.4 mole; in 1470 ml of $CHCl_3$ and 147 ml of EtOH), with swirling during 20 min. After 48 hr at ~5°, the mixture was washed with 10% KOH aq (250 ml × 4), water (250 ml × 2) and brine. Solvent was removed at below 20° to furnish a semisolid, which was triturated with light petroleum (10 ml) and the solid (26 g) collected by filtration; recrystallisation from light petroleum furnished white prisms of 3-hydroxylongifolaldehyde, 21.0 g, m.p. 106–107°, $[\alpha]_D$ −6.4° (*c* 5.03%). PMR ($CCl_4$): three Me–C– (3H, s, 0.97 ppm; 6H, s, 1.03 ppm), –C–C$\underline{H}$O (1H, s, 11.13 ppm). Mass: *m/e* 236 ($M^+$, 100%), 208 (67%), 207 (90%), 177 (55%), 151 (57%), 137 (64%), 123 (58%), 121 (53%), 109 (64%), 97 (56%) and 95 (60%). (Found: C, 76.65; H, 10.07. $C_{15}H_{24}O_2$ requires: C, 76.22; H, 10.24%).

*Semicarbazone* (pyridine method), white microcrystals from EtOH-pyridine, m.p. 210°. (Found: N, 14.00. $C_{16}H_{27}O_2N_3$ requires: N, 14.32%).

2,4-*Dinitrophenylhydrazone* ($H_2SO_4$ method), orange microcrystals from EtOAc, m.p. 200–201°. (Found: N, 13.61. $C_{21}H_{28}O_5N_4$ requires: N, 13.45%).

### *Longicamphenilone* (5)

(a) *Periodate cleavage of* **4**. Compound **4** (8.2 g) in MeOH (205 ml) was treated with $H_5IO_6$ (8.2 g) in $H_2O$ (33 ml) at ~25° for 16 hr in the dark. Usual work-up gave, after solvent removal, a product (7.5 g), which was filtered through $Al_2O_3$/I (200 g) using light petroleum as a solvent and, then recrystallised from aq. EtOH to furnish **5** (5.8 g), m.p. 50–51°, m.m.p. with an authentic sample was undepressed.

(b) *Baeyer–Villiger oxidation of* **4**. Compound **4** (7.08 g) in $CHCl_3$ (20 ml) was cooled (−5°) and treated with a soln of PBA (4.14 g in 75 ml $CHCl_3$ stabilised with 1% EtOH). After 1 hr the mixture was allowed to attain room temp. (~25°) and then kept aside in the dark for 48 hr. The mixture was worked up in the usual manner to give after solvent removal a crystalline mass (6.2 g) which was recrystallised from aq EtOH to give pure **5**, m.p. 50–51°.

### *Rearrangement of* 3-*hydroxylongifolaldehyde to* α-*ketol* **10**

Hydroxylongifolaldehyde (1.0 g) in $CHCl_3$ (10 ml) was treated with *p*-toluenesulfonic acid (0.1 g) at room temp (~25°). After 0.5 hr the reaction was complete (TLC: solvent, 20% EtOAc in $C_6H_6$), when it was diluted with $CHCl_3$ (25 ml), washed with 10% $Na_2CO_3$ aq (50 ml) and then with brine. Removal of solvent gave a product (PMR: C$\underline{H}$OH, s, 3.82 ppm) which was acetylated (4 ml $Ac_2O$, 4 ml pyridine, room temp., 18 hr) and then distilled, after work-up, to give the *keto-acetate* (PMR: singlet at 5.08 ppm, no signal at 5.60 ppm; cf.[3]). Recrystallisation from MeOH yielded crystals, m.p. 91–92°. PMR ($CCl_4$): three $CH_3$–C– (3H singlets at 1.02, 1.05 and 1.11 ppm), $OCOCH_3$ (3H, s, 2.11 ppm), –COC$\underline{H}$ (1H, m, 2.85 ppm), –C$\underline{H}$OAc (1H, s, 5.08 ppm). IR (Nujol): C=O 1735,

---

†We find that oxidation of longifolene with three molar equivalent of PBA gives, besides longicamphenilone (major) a mixture of ketols **6** and **10**, in which ketol **6** is clearly the major component.

1700 cm$^{-1}$. (Found: C, 73.19; H, 9.70. $C_{17}H_{26}O_3$ requires: C, 73.34; H, 9.42%).

*Longidione* (**11**) *from* 3-*hydroxylongifolaldehyde*

3-Hydroxylongifolaldehyde (1.18 g), powdered $Cu(OAc)_2$ (3.0 g) and AcOH aq (70%, 30 ml) were mixed, refluxed (3 hr) and then diluted with water (150 ml) and the product taken up in light petroleum (50 ml × 3), which was washed (10% HCl aq, 25 ml; brine). Solvent removal gave a solid which crystallised from aq EtOH in needles, m.p. 93–94° (cf.[2]).

*Action of LAH on* 3-*hydroxylongifolaldehyde*

To a stirred slurry of LAH (2.0 g) in dry ether (150 ml) was introduced, under the usual conditions, a soln of hydroxylaldehyde (11.8 g) in ether (150 ml), at a rate such that ether reflux was gentle (15 min). The mixture was next refluxed for 18 hr and cautiously decomposed with water (5 ml) in the usual manner. Routine work-up yielded a thick liquid (11.4 g) showing 3 major spots on TLC (solvent: 20% EtOAc in $C_6H_6$). This mixture (11.0 g) was chromatographed (silica gel, dry column[9]) using the TLC solvent system:

| | | |
|---|---|---|
| Frac. 1 (top) | 0.095 g | Solid (**12**) |
| Frac. 2 | 0.434 g | Mixture of **12** and **7** |
| Frac. 3 | 3.811 g | Solid, essentially pure **7** |
| Frac. 4 | 3.341 g | Mixture of **7** and **6** |
| Frac. 5 | 3.077 g | Almost pure **6** |

Frac. 1 was recrystallised from MeCN to furnish pure **12**, m.p. 149–151°. IR (Nujol): OH 3300, 1060 cm$^{-1}$. PMR ($CCl_4$): three $\mathrm{Me{-}\overset{|}{\underset{|}{C}}{-}}$ (3H singlets at 0.99, 1.01 and 1.03 ppm), two $-\underset{|}{\mathrm{C}}\mathrm{HOH}$ (1H, d, 3.13 ppm, J = 10 Hz; 1H, m, 3.70 ppm). (Found: C, 75.28; H, 10.85. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

Frac. 3 was twice recrystallised from MeCN to furnish white needles (2.55 g) of 3-*hydroxylongifolol* (**7**), m.p. 135–136°, $[\alpha]_D$ +5.2° (*c* 5.03%). IR (Nujol): OH 3600, 3250, 1060, 990 cm$^{-1}$. PMR ($CCl_4$): three $\mathrm{\underline{M}e{-}\overset{|}{\underset{|}{C}}{-}}$ (3H singlet at 0.95, 0.98 and 1.03 ppm), $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{{-}C\underline{H}_2OH}$ (2H, AB-q, 3.75, J = 10 Hz, νAB/J = 0.76). Mass: *m/e* 238 ($M^+$, 9%), 207 (89%), 109 (85%), 95 (84%), 87 (52%), 86 (45%), 83 (53%), 81 (68%), 69 (100%), 67 (62%) and 55 (81%). (Found: C, 75.26; H, 10.81. $C_{15}H_{26}O_2$ requires: C, 75.58; H, 11.00%).

Frac. 5 (1.24 g) was acetylated (3 ml $Ac_2O$, 3 ml pyridine, 20 hr at room temp.) to give a product which was recrystallised from MeOH to yield white needles (m.p. 115–116°) of *acetate* of **6**. IR (Nujol): C=O 1735, 1710 cm$^{-1}$. PMR ($CCl_4$): three $\mathrm{Me{-}\overset{|}{\underset{|}{C}}{-}}$ (3H singlets at 1.06, 1.15 and 1.21 ppm), $\mathrm{OCOC\underline{H}_3}$ (3H, s, 2.11), $-\underset{|}{\mathrm{C}}\mathrm{\underline{H}OAc}$ (1H, d, 5.61 ppm, J = 4 Hz). (Found: C, 73.80; H, 9.17. $C_{17}H_{26}O_3$ requires: C, 73.34; H, 9.42%).

*Correlation of* 3-*hydroxylongifolaldehyde with longifolene epoxide*

3-*Hydroxylongifolyl mesylate* (**8**). Compound **7** (1.2 g) in dry pyridine (15 ml) was cooled (0°) and treated with mesyl chloride (freshly distilled over $P_2O_5$, 1.2 ml) and after 1 hr left aside at room temp. (25–28°) for 18 hr. Usual work-up, after solvent (ether) removal at reduced pressure, gave a gum which crystallised from ether-light petroleum: white prisms (0.447 g), m.p. 85–86°. IR (Nujol): OH 3480, 3400 cm$^{-1}$; $-SO_2$ 1170, 1180 cm$^{-1}$. PMR ($CCl_4$): three $\mathrm{CH_3{-}\overset{|}{\underset{|}{C}}{-}}$ (3H singlets at 0.98, 1.02 and 1.03 ppm), $-\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{{-}C\underline{H}_2OSO_2Me}$ (2H, s, 4.4 ppm), $\mathrm{-CH_2OSO_2Me}$ (3H, s, 3.02 ppm). (Found: C, 60.96; H, 8.42. $C_{16}H_{28}O_4S$ requires: C, 60.74; H, 8.92%).

*Longifolene epoxide* (**2**). To a stirred slurry of LAH (1.2 g) in dry ether (50 ml) was slowly added a soln of the above mesylate (0.59 g) in ether (50 ml) at room temp. (27°). The mixture was stirred under reflux (16 hr), cooled and cautiously treated successively with cold water (1.2 ml), 15% NaOH aq (1.2 ml) and water (3.6 ml). After an additional 15 min stirring, the ppt was filtered and washed with ether (50 ml). Usual work-up of the combined ether soln gave a solid (0.42 g), which was recrystallised from light petroleum (at −10°) to furnish crystals (0.28 g), m.p. 41–42°.

## REFERENCES

[1] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115 (1954).

[2] U. R. Nayak and Sukh Dev, *Tetrahedron* **19**, 2269 (1963).

[3] J. Lhomme and G. Ourisson, *Bull. Soc. Chim. Fr.* 1888 (1964).

[4] U. R. Nayak and Sukh Dev, *Tetrahedron* **19**, 2293 (1963).

[5] G. Ourisson, *Bull. Soc. Chim. Fr.* 895 (1955).

[6] Several examples of resistance of sterically shielded 1,2-epoxides to hydride attack are known. See, e.g.: R. N. Moore, C. Golumbic and G. S. Fisher, *J. Am. Chem. Soc.* **78**, 1173 (1956); G. D. Meakins and J. S. Stephenson, *J. Chem. Soc.* 526 (1958); G. Buchi, R. E. Erickson and N. Wakabayashi, *J. Am. Chem. Soc.* **83**, 927 (1961).

[7] For a recent survey see: S.-C. Chen, *Synthesis* 691 (1974).

[8] I. M. Kolthoff, T. S. Lee and M. A. Mairs, *J. Poly. Sci.* 199 (1957).

[9] B. Loev and K. M. Snader, *Chem. & Ind.* 15 (1965).