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STUDIES IN SESQUITERPENES—XXI

LONGIFOLIC ACIDS*

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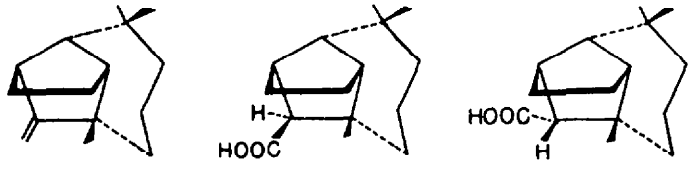
Abstract—The nature and inter-relationship of longifolic acids have been clarified. There are, in fact, three C_{15} monocarboxylic acids derived from longifolene and not two. The acid, described as longifolic acid and obtained in a state of purity for the first time by Naffa and Ourisson, has been shown as not representing the thermodynamically less stable epimer of the well-characterized isolongifolic acid but to possess a different structure, and has been termed ψ-longifolic acid. The less stable epimer, longifolic acid, has been obtained pure for the first time.

SIMONSEN[1] has reported that chromium trioxide–acetic acid oxidation of longifolene gave an acid termed longifolic acid, while sodium dichromate in sulphuric–acetic acid yielded its stabler epimer, isolongifolic acid. Later still, a third acid, α-longifolic acid was isolated[2] by the ozonation of longifolene. By conducting the chromic acid–acetic acid oxidation of longifolene as detailed in the Experimental, all these acids have been isolated from the oxidation mixture. Simonsen regarded these acids as possessing the molecular formula, $C_{14}H_{22}O_2$.

Naffa and Ourisson,[3] showed that these are $C_{15}H_{24}O_2$ acids, formed by the terminal oxidation of longifolene and as such only two epimeric acids are possible. They further found that while isolongifolic acid can be readily obtained pure, longifolic acid obtained by Simonsen was contaminated with its epimer and, a pure sample of "longifolic" acid can only be obtained with great difficulty; α-longifolic acid was considered to be a molecular compound (1:1) of isolongifolic and "longifolic acid".

Zeiss and Arakawa[4] independently arrived at a similar conclusion about the nature of longifolic acids by a study of the lithium aluminium hydride reduction products of these acids or their methyl esters. More recently Ogura[5] adduced further evidence in support of the epimeric nature of isolongifolic and longifolic acids.



I II III

* Communication No. 608, National Chemical Laboratory, Poona.

[1] J. L. Simonsen, *J. Chem. Soc.* **123**, 2642 (1923).
[2] A. E. Bradfield, E. M. Francis and J. L. Simonsen, *J. Chem. Soc.* 188 (1934).
[3] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115 (1954).
[4] H. H. Zeiss and M. Arakawa, *J. Amer. Chem. Soc.* **76**, 1653 (1954).
[5] I. Ogura, *Bull. Chem. Soc., Japan* **29**, 363 (1956).

Based on the structure (I)[6,7] of longifolene, isolongifolic and longifolic acids have been represented as II and III[8] respectively.

In the course of our studies[9] on the peracid oxidation of longifolene, we had occasion to isolate a longifolic acid which from its physical characteristics could be identified with the α-longifolic acid of Simonsen. However, a comparison of its specific rotation with that of longifolic and isolongifolic acids cast a doubt on its formulation as a molecular compound of the two so-called epimeric acids. In order to examine this point critically, authentic samples of isolongifolic and longifolic acids were prepared by known procedures.[1,3] Some physical characteristics of these three acids have been recorded in Table 1 and the data compared with those of other workers. It is at once apparent that α-longifolic acid with $[\alpha]_D$ −24° cannot be a mixture of isolongifolic ($[\alpha]_D$ −10°) and longifolic acid ($[\alpha]_D$ +8), and, in fact, a synthetic mixture (1:1) of the two latter acids had the expected mean rotation.

TABLE 1. SOME CHARACTERISTICS OF LONGIFOLIC ACIDS* PREPARED BY VARIOUS WORKERS

Author (Reference)	Isolongifolic		α-Longifolic		Longifolic	
	m.p.°	[α]° †	m.p.°	[α]°	m.p.°	[α]°
1	136	−13(g)	140–142	−31(g)	152–153	0
3	135–135·5	−12(g)	139·5–140·5	−34(g)	169–171	—
4	136	—	140–142	—	152–153	−6
Present	136–137	−10	139–140	−24	160–161·5	+8

* Names as given in literature; for corrected nomenclature see Table 2.

† Specific rotations are all taken in ethanol and are for the sodium D line (not indicated) or for the mercury green line (5461 A°; marked g). The values have been corrected to the nearest integer.

At this stage it became necessary to consider the homogeneity of these preparations. Gas liquid chromatography (GLC; Fig. 1) of their methyl esters, in conjunction with a critical study of their IR spectra, provided the necessary answer. Methyl isolongifolate was found to be 100% pure, while "methyl longifolate" (from acid, m.p. 160–161·5°) turned out to be a two-component mixture with methyl isolongifolate constituting ~27%. "Methyl α-longifolate" (from acid m.p. 139–140°) also showed two components in almost equal proportions, and methyl isolongifolate was identified as one of these. Though, the major constituent of "methyl longifolate" and the unknown constituent of "methyl α-longifolate" had the same retention time, the two, as will be shown now, are different. Thus we are dealing with three acids and not two as concluded by others earlier. Methyl longifolate was next purified by gas-chromatography and the ester, thus freed from methyl isolongifolate, on hydrolysis furnished a pure acid, m.p. 171–172°. It would appear that this acid had been obtained earlier, in a more or less pure state, by Naffa and Ourisson.[3] but it has been demonstrated now (*vide infra*) that this is not epimeric with isolongifolic acid. The unknown component of "methyl α-longifolate" could be obtained pure either by preparative GLC or by partial esterification of "α-longifolic acid" as described under Experimental; the pure acid had m.p. 143–144°.

[6] R. H. Moffett and D. Rogers, *Chem. & Ind.* 916 (1953).

[7] P. Naffa and G. Ourisson, *Chem. & Ind.* 917 (1953).

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

[9] U. R. Nayak and Sukh Dev, *Tetrahedron*, paper XIX of this series (1963).

After having established the fact that three C_{15} acids can be obtained by the oxidation of longifolene, the question arose, which two of these represent the epimeric pair expected from longifolene (I). Naffa and Ourisson[3,8] have clearly demonstrated that the acid of m.p. 136–137° has the structure II. To pin down the second epimer

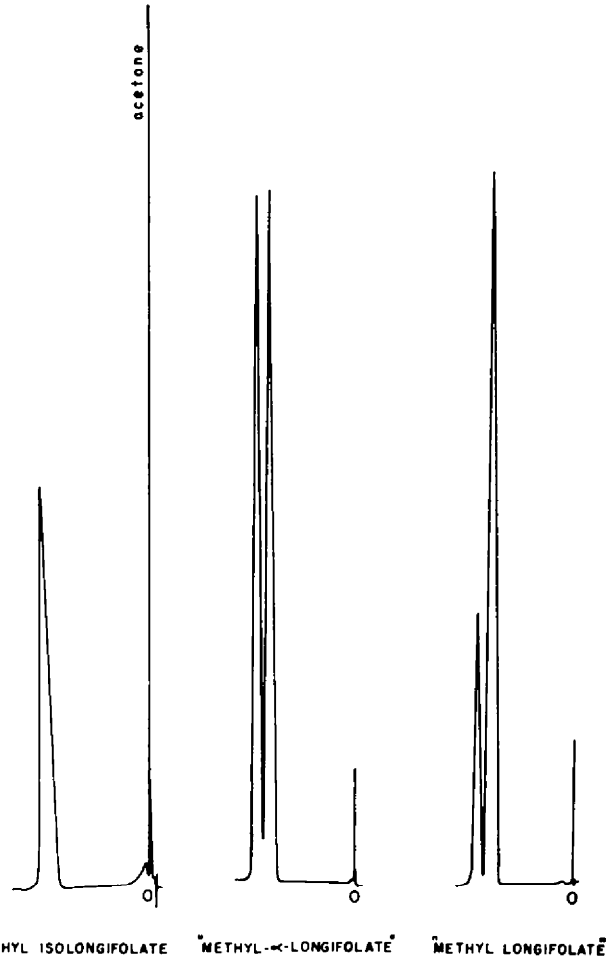


FIG. 1. Gas liquid chromatography of longifolic acid esters.

out of the remaining two acids, base-catalysed epimerization of their methyl esters has been investigated. Apparently both "α-longifolic acid" (m.p. 140–141°)[1,3] and "longifolic acid" (of m.p. 152–153°[10])[1] have been claimed to undergo epimerization to isolongifolic acid. The methyl ester from the pure acid of m.p. 143–144° (obtainable from "α-longifolic acid") on epimerization with sodium methoxide in methanol underwent quantitative isomerization to isolongifolate whereas the ester from acid of m.p. 171–172° (obtainable from "longifolic acid") was unaffected under

[10] The so-called longifolic acid of this m.p. should, according to present work, contain ~40% isolongifolic acid. After heating this product with hydrobromic acid in a sealed tube at 200° for 4 hr, isolongifolic acid, in an unspecified yield, was obtained.[1] No importance can be attached to this experiment in view of heavy contamination of the starting material with isolongifolic acid.

these conditions. Thus, the acid of m.p. 143–144° is the pure unstable epimer (III), while the so-called "longifolic acid" must possess a different structure.

In view of the above, it is necessary to correct the nomenclature. Some of the properties of these acids have been collected in Table 2 and the IR spectra of their

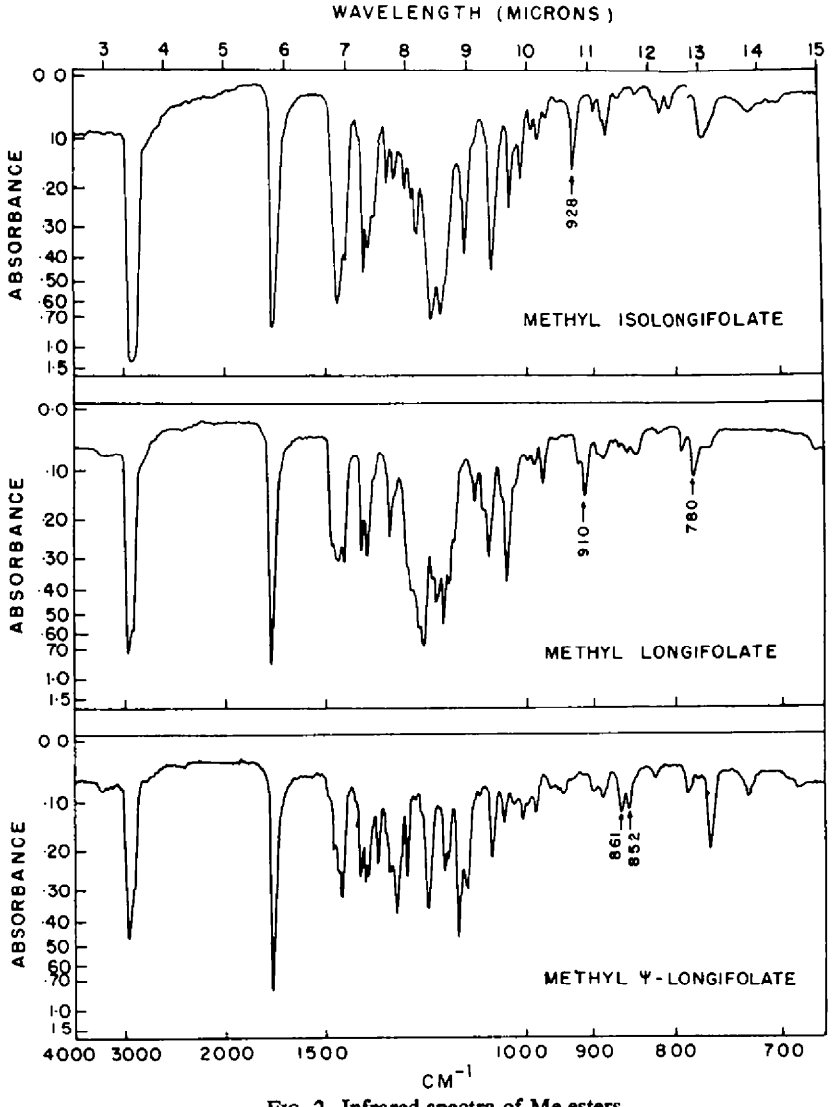


FIG. 2. Infrared spectra of Me esters.

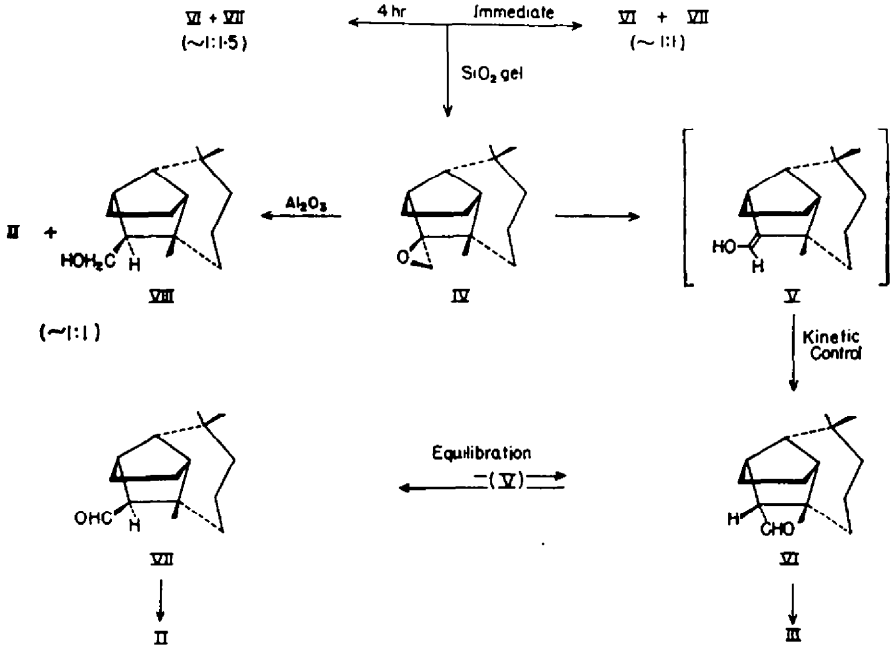
methyl esters are shown in Fig. 2. It is proposed that the acid of m.p. 143–144° should be termed longifolic acid, while acid of m.p. 171–172° be designated ψ-longifolic acid, as it does not possess the structure so far attributed to it and, in all probability, belongs to longicyclene series.[11] The acid of m.p. 136–137° retains the structure and name (isolongifolic acid) so far assigned to it.

[11] For longicyclene see: U. R. Nayak and Sukh Dev, *Tetrahedron Letters* 243 (1963). The structure of this acid would be subject matter of a future publication.

TABLE 2. PROPERTIES OF PURE LONGIFOLIC ACIDS

	Epimeric Pair		ψ-Longifolic Acid
	Longifolic Acid (III)	Isolongifolic Acid (II)	
m.p.	143–144°	136–137°	171–172°
$[\alpha]_D^{26°}$, EtOH	−32·6 (c = 5·83%)	−10·2 (c = 5·31%)	+18·3 (c = 4·49%)
$\nu_{CCl_4}^{C=O}$ (cm^{-1})	1692	1700	1710
Methyl Ester			
b.p.	117–118°/2 mm	148–149°/6 mm	120°/2 mm
m.p	—	55–56°	—
$n_D^{20°}$	1·4965	—	1·4971
$[\alpha]_D^{26°}$	−32·0 (c = 5·35%)	+6·5 (c = 5·20%)	+20·6 (c = 3·30%)
$\nu_{CCl_4}^{C=O}$ (cm^{-1})	1725	1740	1720

The structures II and III for the epimeric acids have been further confirmed in the following manner. The preparation of longifolene epoxide (IV)[9] was used to prepare longifolic and isolongifolic acids in a stereoselective manner. In an isomerization of an α-epoxide to an aldehyde or ketone, the protonation of the intermediate enol preferentially takes place from the less-hindered face of the molecule.[12–14] Thus proton-addition to the enol (V) in the longifolene series should, preferentially, occur from the



[12] H. E. Zimmerman, *J. Org. Chem.* **20**, 549 (1955); *J. Amer. Chem. Soc.* **78**, 1168 (1956); **79**, 5554 (1957),

[13] H. E. Zimmerman and H. J. Giallombardo, *J. Amer. Chem. Soc.* **78**, 6259 (1956).

[14] H. E. Zimmerman and T. W. Cutshall, *J. Amer. Chem. Soc.* **80**, 2893 (1958); **81**, 4305 (1959).

less-hindered β-face to furnish, under non-equilibrating conditions, the less stable longifolaldehyde (VI). However, if equilibration at the aldehyde stage is permitted, the thermodynamically more stable isolongifolaldehyde (VII) should result. The two aldehydes could then be converted to the respective acids (III) and (II).

In actual practice only partial control at the equilibration stage could be maintained but the results obtained support the structures assigned to the epimeric acids. When an hexane solution of the epoxide was passed through a short column of washed silica gel, isomerization[15] to the aldehydes took place. Air oxidation[16] of the aldehydes gave a mixture of longifolic and isolongifolic acids, the composition of which was established by GLC of their methyl esters. The ratio of these acids was dependent on the residence time of the material on the column. For example, if after adsorption, the product was eluted out immediately, the aldehyde mixture after oxidation yielded longifolic and isolongifolic acids in the ratio 1:1, whereas if the elution was delayed for 4 hr, the ratio of the longifolic acid to its epimer changed to 1:1·5. On the basis of these results, it was argued that adsorption on a column of alumina[15,17], where equilibration would be favoured, would lead essentially to the more stable isolongifolaldehyde. In practice, when the epoxide was adsorbed on a column of neutral alumina of Brockmann grade I and eluted after 21 hr, isolongifolol (VIII) and isolongifolic acid (ratio ~1:1) were obtained in almost quantitative yield. Thus, the expected equilibration did take place, but isolongifolaldehyde was intercepted by a Canizzaro-type reaction[18] to give the corresponding alcohol and the acid.

EXPERIMENTAL

All m.ps. and b.ps. are uncorrected. Solvent extracts were finally washed with brine and dried (Na_2SO_4). Optical rotations were measured in ethanol unless stated to the contrary. The IR spectra were taken on a Perkin-Elmer Infracord model 137E spectrophotometer, either as smears (liquids) or in Nujol (solids), unless specified otherwise.

Longifolic acid

(i) The acid mixture (2·36 g; the so-called 'α-longifolic acid'; m.p. 139–140°, $[\alpha]_D$ −24·4°; approximately 1:1 mixture as shown by GLC; obtained during the perbenzoic acid oxidation[9] of longifolene) was mixed with methanol (5 ml), benzene (6 ml) and conc H_2SO_4 (0·7 ml) and refluxed for 30 hr. The product was worked up as described under (ii) to yield an ester (1·80 g; shown by GLC to contain 82% methyl isolongifolate) and an unesterified acid (0·79 g) m.p. ~135°; this after two recrystallizations from aceto-nitrile gave glistening white flakes m.p. 143–144°.

(ii) To a stirred solution of longifolene[19] (200 g) in glacial acetic acid (1 l.) was added dropwise, a solution of CrO_3 (400 g) in water (270 ml) and conc H_2SO_4 (10 ml), the temp being maintained ~45° by external cooling. After the addition had been completed (2 hr), the reaction mixture was warmed on the water bath (1 hr). The green oxidation mixture was worked up by diluting with water (2 l.),

[15] During the attempted purification of crude epoxide by column chromatography it was observed[9] that it rearranged to aldehydes over various adsorbents.

[16] Air oxidation was preferred for oxidation to the acid, as no epimerization of the aldehyde is to be expected under these conditions.

[17] Isomerization of α-epoxides to the carbonyl compounds during chromatography over alumina has been reported: G. Büchi, R. E. Erickson and N. Wakabayashi, *J. Amer. Chem. Soc.* **83**, 927 (1961)

[18] Though, Canizzaro reaction [T. A. Geissman in R. Adams *Organic Reactions* II, pp. 94–113. John Wiley, New York (1946)] is, ordinarily, restricted to aldehydes that are devoid of an α-hydrogen, other aldehydes may also undergo this reaction, if the α-position is sufficiently hindered to inhibit the competing aldol-type condensation under those conditions.

[19] Longifolene was isolated as described elsewhere: U. R. Nayak and Sukh Dev, *Tetrahedron* **8**, 42 (1960).

extracting with benzene (300 ml × 5) and separating the acid portion by extraction with 10% NaOH aq. (200 ml × 5). Acidification of the alkaline extracts yielded the crude acids as a pale yellow solid (76·9 g), m.p. 110–116°.

A mixture of the above product (236 g), abs. methanol (472 ml), benzene (590 ml) and conc H_2SO_4 (70 ml) was refluxed for 70 hr. The product was diluted with water (750 ml), the benzene layer separated and the aq. part extracted with ether (100 ml × 4). The combined organic phase was repeatedly extracted with a saturated Na_2CO_3 aq. The latter, after treatment with charcoal, was acidified (HCl) yielding a solid (19 g), m.p. ~124°; 3 recrystallizations from aq. ethanol and one from acetonitrile gave colourless shining flakes (4·1 g), m.p. 143–144°. (Found: C, 76·3; H, 10·1. $C_{15}H_{24}O_2$ requires: C, 76·2; H, 10·2%).

Its *methyl ester* (diazomethane method in ether) was obtained as a colourless oil, b.p. 117–118°/2 mm (Found: C, 77·1; H, 10·6. $C_{16}H_{26}O_2$ requires: C, 76·7; H, 10·5%).

Isolongifolic acid

The solvent extract from the above esterification was evaporated yielding the crude esters mixture (214 g) which was diluted with n-hexane (50 ml), chilled in a freezing mixture and the crystalline *methyl isolongifolate* (~63 g) collected, m.p. ~53°; recrystallization from methanol yielded colourless needles, m.p. 55–56°, with little loss.

Methyl isolongifolate (m.p. 55–56°; 17·5 g), KOH (6 g), water (10 ml) and ethanol (90 ml) were refluxed on a steam-bath for 6 hr. After dilution with water, the reaction mixture was extracted with ether (50 ml) and the cooled aq. part acidified to give isolongifolic acid (12·5 g), m.p. 134–136°, which recrystallized from acetic acid in colourless plates, m.p. 136–137°.

ψ-Longifolic acid.

The mother liquor, after separation of the crystalline methyl isolongifolate was freed of solvent, and the liquid residue (139 g) was carefully fractionated in a packed (glass helices) column fitted with a total condensation partial take-off type still head. The first fraction (42·5 g), b.p. 140–142°/6 mm, n_D^{28} 1·4975 and α_D +9° (neat), was enriched methyl ψ-longifolate while the second fraction (52·1 g), b.p. 148–149°/6 mm, crystallized completely and was identified as methyl isolongifolate.

Crude methyl ψ-longifolate (17·5 g) was hydrolysed for 18 hr with alcoholic alkali as described for methyl isolongifolate. This gave an acid (13·8 g), m.p. 151–155°, which was recrystallized thrice from acetic acid giving colourless prisms, m.p. 160–161·5°, $[\alpha]_D$ +8° (*c*, 5·1%), yield 2·79 g. GLC of its methyl ester [b.p. 118–119°/2 mm, $[\alpha]_D$ +16·9° (*c*, 4·7%)] showed it to be a mixture of ψ-longifolic acid (75%) and isolongifolic acid (25%). Since, further purification of the acid could not be achieved by crystallizations, its methyl ester (diazomethane method) was separated by preparative GLC into methyl ψ-longifolate (b.p. 120°/2 mm, n_D^{30} 1·4971) and methyl isolongifolate (identified by m.p., mixed m.p. and IR spectrum). Hydrolysis of ψ-longifolate (300 mg) with aq. ethanolic KOH (300 mg in 5 ml) for 4 hr at reflux, followed by the usual work-up, gave the acid as a white precipitate (212 mg), m.p. 165–167°; after 2 recrystallizations from acetonitrile, ψ-longifolic acid was obtained as colourless micro prisms (92 mg), m.p. 171–172°. (Found: C, 77·1; H, 9·6. $C_{15}H_{22}O_2$ requires: C, 76·9; H, 9·5%. $C_{15}H_{24}O_2$ requires: C, 76·2; H, 10·2%). Esterification of this material with diazomethane gave gas-chromatographically pure *methyl ψ longifolate* as a colourless liquid, $[\alpha]_D$ +20·6° (*c* = 3·3%) (Found: C, 77·8; H, 10·1. $C_{16}H_{24}O_2$ requires: C, 77·4; H, 9·7%. $C_{16}H_{26}O_2$ requires: C, 76·7; H, 10·5%).

Equilibration of methyl esters

(i) *Methyl longifolate.* Sodium methoxide in methanol (from 0·8 g Na in 20 ml MeOH) was mixed with methyl longifolate (300 mg) in the same solvent (5 ml) and refluxed for 24 hr (anhydrous conditions). The cooled reaction mixture was diluted with water (100 ml) and extracted with ether (25 ml × 3); the extract was washed neutral, dried and the solvent removed yielding a colourless crystalline product (263 mg) m.p. 51–53°, which was shown by GLC to be essentially only methyl isolongifolate; this was recrystallized from methanol to give colourless needles, m.p. 54–55° and identified as methyl isolongifolate by mixed m.p. and IR spectrum.

(ii) *Methyl ψ-longifolate.* This ester (96% purity by GLC; 300 mg) was subjected to equilibrating conditions exactly as described in (i) and worked up yielding a colourless oil (247 mg), b.p. 120°/2·5 mm, which was shown by GLC to be the unchanged starting material.

Reactions of longifolene α-epoxide

Isomerization over silica gel. Longifolene epoxide[9] (300 mg) in hexane (5 ml) was just adsorbed on a short column (6·5 cm × 2·2 cm, prepared in hexane) of washed silica gel[20] and then eluted out with benzene (100 ml). Removal of the solvent from the total eluterate yielded a syrup (280 mg) which from its IR spectrum was found to be completely devoid (absence of the 930 cm^{-1} band[9]) of longifelene epoxide and to have isomerized to aldehydes (2675 and 1710 cm^{-1}). The product was divided into 2 equal parts and one half converted into semicarbazone (sodium acetate method) which was obtained readily in good yield and had m.p. 193–196° (dec.); two recrystallizations from aq. ethanol gave white crystals m.p. 199–201° (dec.) which was raised on admixture with either longifolaldehyde semicarbazone (m.p. 218° dec.)[9] or isolongifolaldehyde semicarbazone (m.p. 217–218° dec.).[9] The second half on keeping aside in the Laboratory had completely changed into a waxy solid during 48 hr (air oxidation to the acids). This was converted into the methyl esters by treatment with diazomethane and the composition estimated by GLC.

Isomerization over alumina. Longifolene epoxide (205 mg) in n-hexane (3 ml) was just adsorbed on a column of neutral alumina grade I (6·0 g; 13 cm × 1 cm) and left overnight (21 hr). Both pet. ether and benzene eluterates (50 ml each) gave no material on evaporation. Elution with 2% methanol in benzene (50 ml) gave a solid (124 mg) m.p. 96–101° which after one recrystallization from pet. ether at 0° yielded colourless rods m.p. 112–113° underpressed upon admixture with an authentic sample of isolongifolol; both had identical IR spectra. Washing the column with 10% Na_2CO_3 aq. (50 ml) eluted an acid, which was isolated by acidification and extraction, as a colourless solid (71 mg) m.p. ~110°. Recrystallization from acetonitrile furnished colourless needles m.p. 136–137° identified as isolongifolic acid by mixed m.p. and preparation of its crystalline methyl ester m.p. 55–56°, undepressed upon admixture with genuine methyl isolongifolate.

Gas liquid chromatography. The GLC were carried out on a Perkin-Elmer Vapour Fractometer model 154D at 200° over 20% diethylene glycol succinate on celite (60–100 mesh) using a carrier gas at 15 lb/sq. in. press. The analytical separations were carried out on a 2 meter column (internal diameter 1/4") using H_2 as the carrier gas. The preparative GLC were carried out on the preparative 3 meter column (supplied by Perkin-Elmer) using N_2 as the mobile phase.

Acknowledgements—The authors thank Mr. R. G. Bhandari and Mr. V. S. Pansare and his colleagues, of the National Chemical Laboratory, for the IR spectra and microanalyses respectively.

[20] Silica gel (−100 to +200 mesh) (200 g) was stirred with distilled water (500 ml × 10), each time decanting the washings after some settling time. Finally it was filtered under suction and dried at 120° for 24 hr. When unwashed activated silica gel was used for the isomerization, more of isolongifolaldehyde was formed.