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TERPENOIDS—LXVI

RING ENLARGEMENT PRODUCED BY THE ALKALINE FUSION OF ω-BROMOLONGIFOLENE*

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Abstract—By analogy with ω-bromocamphene, ω-bromolongifolene on fusion with alkali, but at a comparatively higher temperature, gives several monomeric and dimeric products as a result of ring enlargement. The monomeric products have been characterized as longihomocamphenilone (VIII) and longi-isohomocamphenilone (IX). The dimeric products are composed of a mixture of longifolenyl ethers and the kinetic dimers. Lead tetraacetate oxidation of longifolene, according to the method of Ourisson, has been found to yield, not only longihomocamphenilone and longidione, but also a crystalline alcohol, identified as isolongifolol (XI).

BASE induced ring enlargement of ω-bromocamphene was first studied by Lipp.[1] He observed that potassium hydroxide fusion of ω-bromocamphene affords a six-membered ring ketone and a divinyl ether as a dimeric product. Later, Hückel[2] and Matsubara[3] also investigated these reaction products, but only recently Wolinsky[4] after reinvestigation, characterized the constituents as I to V.

Longifolene (VI), which in many reactions is similar to camphene, also forms ω-bromolongifolene (VII). Ourisson *et al.*[5] attempted alkaline fusion of the ω-bromo compound (VII) without success. A reinvestigation of the alkali fusion of ω-bromolongifolene has produced interesting results which we wish to place on record.

During the initial alkali fusion of ω-bromolongifolene, using the method described by Wolinsky[4] for ω-bromocamphene, the bromo compound was recovered unchanged. Considering the structure of longifolene and its general inertness, it was felt that the conditions for alkali fusion mentioned by Ourisson might not be applicable and hence certain modifications in the reaction were employed. After several attempts by varying the temperature of fusion, it was found that a temperature range of 380 to 400° is required. Instead of glass tubes, a stainless steel tube fitted with a long air condenser was found necessary for the drastic conditions employed.

As in the case of the camphene series, the fusion products were steam distilled and the distillate and the residue worked up separately.

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* Communication number 730 from the National Chemical Laboratory, Poona-8, India.

[1] P. Lipp, *J. Prakt. Chem.* **105**, 50 (1922); P. Lipp, A. Gotzen, F. Reinartz, *Liebigs Ann.* **453**, 1 (1927).

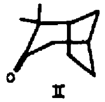
[2] W. Huckel and K. Hartmann, *Ber. Dtsch. Chem. Ges* **70**, 959 (1937); W. Huckel, *Chem. Ber.* **80**, 41 (1947).

[3] Y. Matsubara, *Chem. Abstr.* **51**, 1787 (1957); *Ibid.* **53**, 21716 (1959).

[4] J. Wolinsky, *J. Org. Chem.* **26**, 704 (1961).

[5] G. Dupont, R. Dulou, P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1075 (1954).

I



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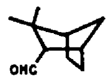
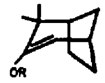
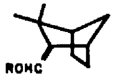


III

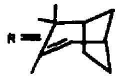
IVa



IVb



IVc



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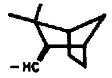
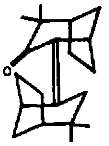
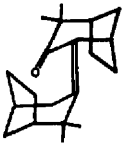
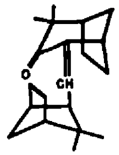




Va



Vb



Vc

Steam distilled products

By judicious application of GLC and TLC, the product was found to be a mixture of four components, the identification of which was carried out by employing both physical and chemical methods. Actual separation of these components was achieved by elution chromatography. Of the four, two were identified as longifolene and unreacted ω-bromolongifolene. The other two were found to be ketones (5–7% yield). IR spectra of these showed close similarity and indicated that both are six-membered ring ketones with a $—CH_2—CO—$ linkage, but they are different as shown by GLC, TLC and NMR studies.

One of the ketones (IR spectra, Fig. 1; NMR spectra Fig. 3) agrees perfectly with the ring enlarged ketone longihomocamphenilone (VIII), prepared by Ourisson[6] by lead tetraacetate oxidation of longifolene. On the basis of chemical and NMR spectral evidence he proved the structure as being VIII;[7] the second ketone (obtained by us) must, therefore, have the structure IX and the name longi-isohomocamphenilone (IR spectra Fig. 1; NMR spectra, Fig. 4) is proposed. In conformity with this, both these ketones give longidione (X) on treatment with selenium dioxide.[6]

While preparing standard longihomocamphenilone (VIII) for comparison purposes by lead tetraacetate oxidation of longifolene according to the procedure of Ourisson,[6] together with longihomocamphenilone (VIII) and longidione (X), substantial amounts (5%) of another compound, an alcohol, which has been characterized as iso-longifolol[6,8] (XI) was isolated. Its identity was further confirmed by oxidation to iso-longifolic acid[8–10] (XII).

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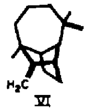
[6] P. Naffa and G. Ourisson, *Bull. Soc. Chim. Fr.* 1115 (1954).
[7] S. Munavalli and G. Ourisson, *Bull. Soc. Chim. Fr.* 726 (1964).
[8] H. H. Zeiss and M. Arakawa, *J. Amer. Chem. Soc.* 76, 1653 (1954).
[9] J. L. Simonsen, *J. Chem. Soc.* 123, 2642 (1923).
[10] U. R. Nayak and Sukh Dev, *Tetrahedron* 19, 2293 (1963).

Residue

The residue from steam distillation of the alkaline fusion product was purified by repeated chromatography and distillation under diffusion pump vacuum and the purity examined by TLC using silica gel impregnated with silver nitrate.[11]

The product was found to be mostly dilongifolenyl ether dimer (XIIIa and b), since it has an absorption maximum at 6·05 μ (1653 cm^{-1}) which supports the presence of a vinyl ether, revealing that the alkaline fusion of VII predominantly produces a unique ring expansion. The ketone dimers (XIVa and b) which as in the camphene series, might also be present, could not be isolated. Although their presence is not supported by UV absorption, a positive indication comes from ozonolysis of the dimeric product, when both the ketones (VIII and IX) and the diketone (X) are produced. The presence of a divinyl ether was established by chromic acid oxidation to furnish longihomocamphenilone (VIII), longi-isohomocamphenilone (IX), longidione (X) and longiforic acid (XV).



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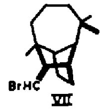
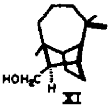


VII

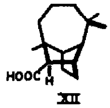
VIII

IX

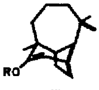
X



XI

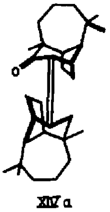


XII

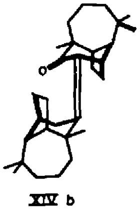


XIIIa

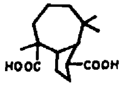
XIIIb



XIVa



XIVb



XV

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Rotations were taken in $CHCl_3$ solution. IR spectra were taken as liquid films for liquids and in nujol for solids on a Perkin-Elmer Model 137B Infracord spectrophotometer by Ms. Gopinath and Deshpande. The NMR spectra were taken in CCl_4 solution using tetramethylsilane as internal standard on a Varian A-60 spectrometer by Dr. Nair and Mr. Mulla. GLC analyses were carried out on a Griffin-George instrument on polyester column using H_2 under press. as the carrier gas by Ms. Bapat and Sankpal. Anhydrous Na_2SO_4 was used for all drying purposes. Microanalyses were carried out by Mr. Pansare and colleagues.

ω-Bromolongifolene (VII). This was prepared according to the procedure of Ourisson with some modifications. To a mechanically stirred solution of longifolene (100 g) in dry ether (300 ml), Br_2 (80 g) in dry ether (500 ml) was added at −10° during 3 hr and further kept at the same temp for ½ hr. The mixture was then kept in a freeze for overnight. The ether was removed in vacuum at 20°, dimethylaniline (200 g, 3 equivs) added and the mixture heated for 7 hr at 180°. It was acidified with

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[11] A. S. Gupta and Sukh Dev, *J. Chromatog.* **12**, 190 (1963).

HCl aq (1:1), extracted with ether, washed thoroughly with water until free of acid, dried, the ether removed and the residue fractionally distilled to yield pure (GLC, TLC) ω-bromolongifolene (43–45%), b.p. 150°/6 mm, m.p. 40–41°. (Found: Br, 27·94. $C_{16}H_{23}Br$ requires: Br, 28·02%).

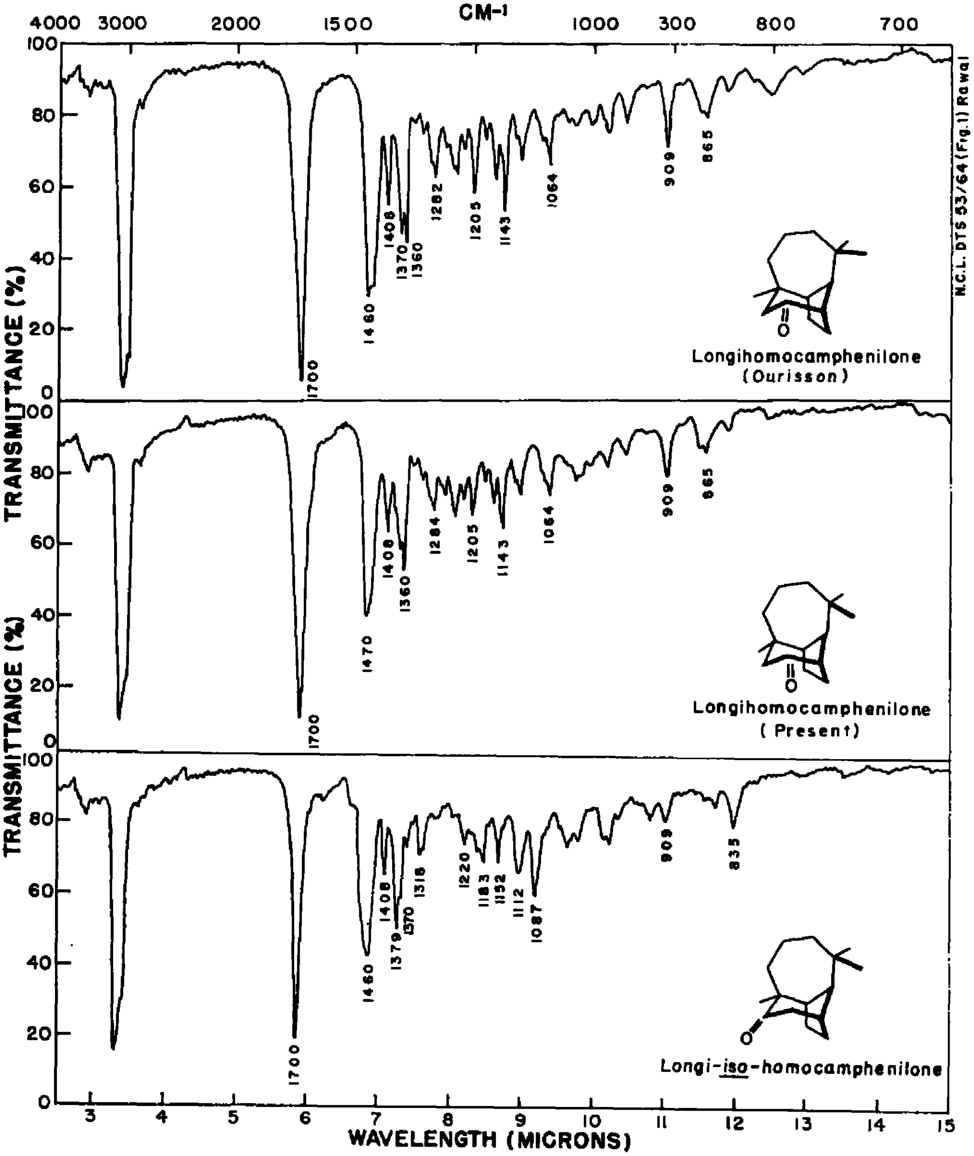

FIG. 1

Fusion of ω-bromolongifolene with potassium hydroxide. ω-Bromolongifolene (2–5 g) and KOH (6–15 g) were placed in a stainless steel tube (length 8", diameter 1") fitted with a long air condenser. The contents were heated on a sand bath and the temp slowly raised to and kept at 380–400° for 1½ hr. After cooling the tube, the contents (dark brown) were poured into water. Several such fusions (from 90 g of VII) were combined together and steam distilled. The distillate and the residue were worked up separately.

Longihomocamphenilone (VIII) *and longi-isohomocamphenilone* (IX). The steam distillate was extracted with ether, washed, dried and the ether removed. The residue (22·5 g) was chromatographed on alumina (gr. I, 675 g) and eluted successively with pet. ether, benzene and ether.

Pet. ether eluate (15·5 g) was found to contain a mixture of longifolene and unreacted ω-bromolongifolene, which were separated by repeated chromatography and characterized by GLC, TLC and IR analyses.

The earlier fractions of the benzene eluates and the later fractions of the ether eluates were rich in the ketones (IX and VIII) respectively. The intermediate fractions were a mixture of these two ketones. By careful and repeated chromatography of the appropriate fractions, these two ketones were obtained in the pure form (GLC and TLC) and were further purified by sublimation.

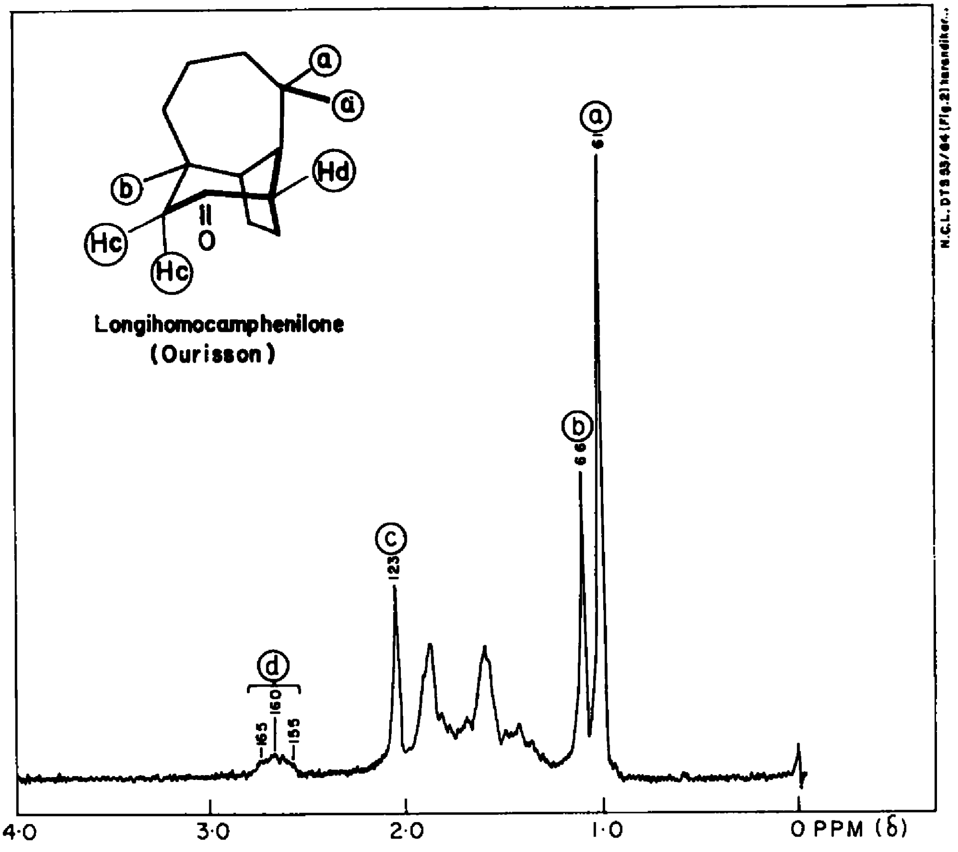

Fig. 2

Longihomocamphenilone (VIII; yield 2 g). It had m.p. 55–57°, $(\alpha)_D$ + 91·26° (*c*, 7·15). (Found: C, 82·04; H, 10·64. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). 2,4-DNP derivative, m.p. 144°. (Found: N, 14·23. $C_{21}H_{28}O_4N_4$ requires: N, 14·01%).

The same ketone prepared from longifolene by treatment with lead tetraacetate according to the method of Ourisson showed the same m.p. (55–57°) but a higher specific rotation (+141·6°). The m.ps of the DNPs of our ketone (144°) and the Ourrison's ketone, as obtained by us (144–145°), were also somewhat lower than observed by Ourrisson (156–158°). However, GLC and TLC behaviour and the IR and the NMR spectra of our ketone were identical with Ourrison's ketone, thus proving their identity. It may be possible that partial racemization has taken place during high temp alkali fusion which will explain the lower optical rotation.

Longi-isohomocamphenilone (IX, yield 2 g). It had m.p. 52–53°, $(\alpha)_D$ +64·13° (*c*, 1·45). (Found: C, 82·08; H, 10·79. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%). 2,4-DNP derivative, m.p. 166°. (Found: N, 14·45. $C_{21}H_{28}O_4N_4$ requires: N, 14·01%).

Selenium dioxide oxidation of longihomocamphenilone (VIII) *and longi-isohomocamphenilone* (IX) *to longidione* (X). A solution of SeO_2 (150 mg) in a few drops water and acetic acid (2 ml) was added to a solution of longi-isohomocamphenilone (56 mg) in glacial acetic acid (2 ml) at 80° and the mixture heated on a water bath for 24 hr. It was then diluted with water, extracted with ether, the ether extract washed with water, dried and the ether removed. The solid diketone was crystallized from pet. ether as fine yellow crystals; yield 50 mg, m.p. 93–94°, mixed m.p. with authentic sample undepressed. IR bands at: 2960; 1730 and 1700 (doublet), 1497 and 1370 cm⁻¹. (Found: C, 77·05; H, 9·61. $C_{15}H_{22}O_2$ requires: C, 76·88; H, 9·46%).

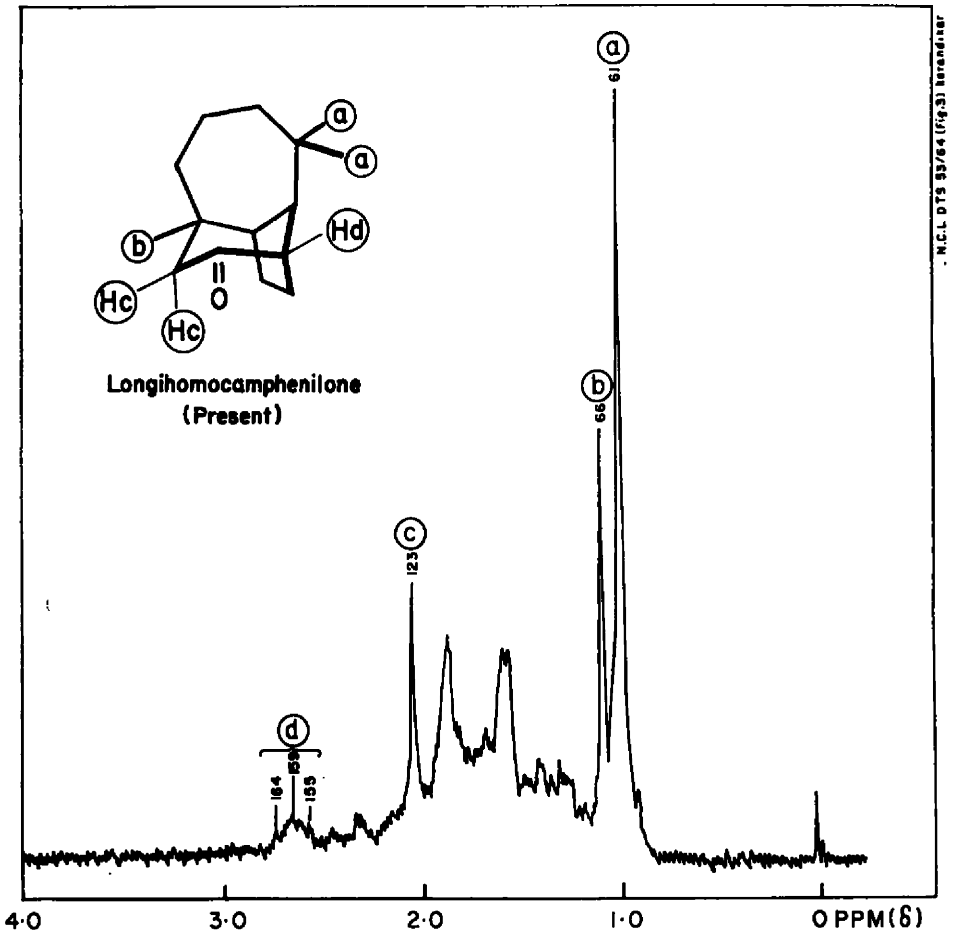

FIG. 3

The similar oxidation of longihomocamphenilone (VIII) gives the same product.

Dilongifolenyl ether (XIII a, b). The residue from steam distillation of the alkaline fusion products was extracted with ether, washed with water till neutral, dried and the ether removed to yield a viscous dark brown product (35 g). It was chromatographed over alumina (Gr.II, 1 kg). On distillation it afforded a viscous, light yellow oil, b.p. 215° (bath)/1·54 × 10^{-2} mm; IR bands at: 2941, 1653, 1449, 1370, 1205, 1176, 1156, 1130, 1093, 1036, 980, 926, 830 and 820 cm⁻¹. (Found: C, 85·92; H, 11·18. $C_{30}H_{46}O$ requires: C, 85·24; H, 10·97%).

Chromic acid oxidation of dilongifolenyl ether

The ether (2·5 g) and CrO_3 (1·7 g) in acetic acid (18 ml) were heated on a water bath for 1 hr. Potassium carbonate (20 g) was added to the green solution and the mixture steam distilled. The distillate was extracted with ether affording a yellowish oil (0·7 g), shown to be a mixture of longihomocamphenilone, longi-isohomocamphenilone and longidione by GLC and TLC analyses and further confirmed by actual isolation via chromatography over alumina.

The residue left after steam distillation of the product of chromic acid oxidation was made slightly acidic. The organic material was extracted with ether and divided by treatment with alkali into acidic and neutral portions. The former, which was composed of longiforic acid (XV), was crystallized from ethyl acetate, m.p. 220–221°.

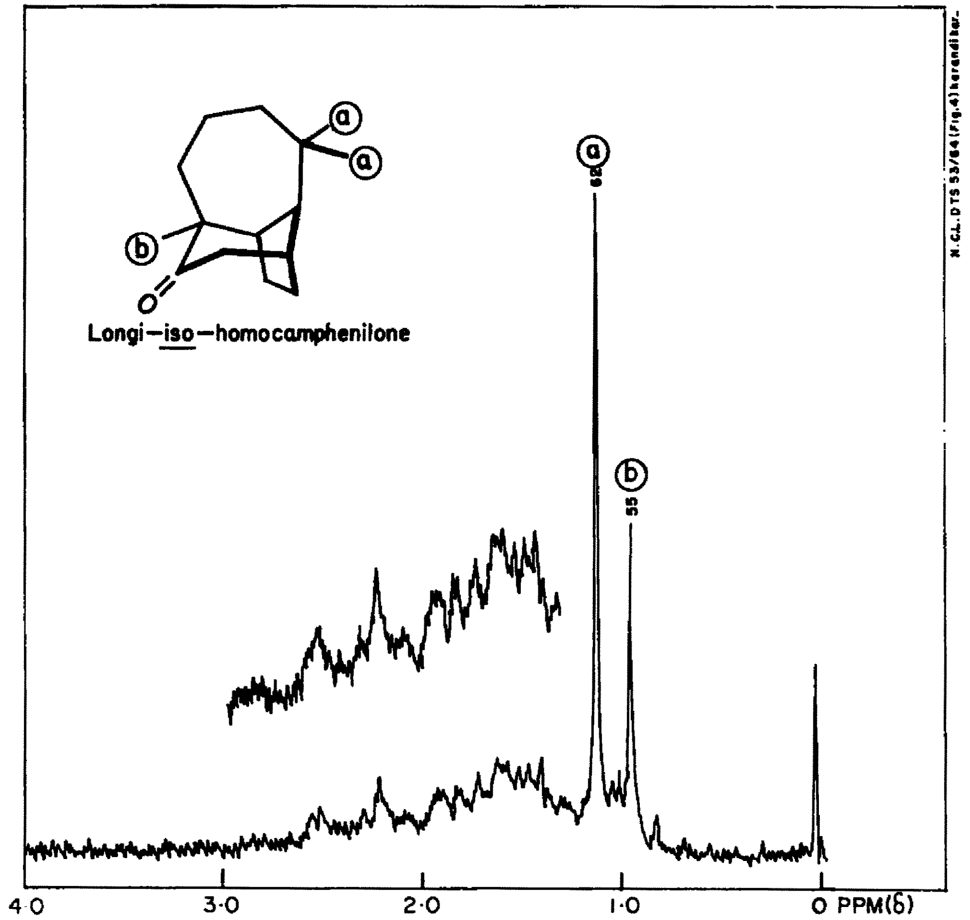

Fig. 4

Ozonolysis of dilongifolenyl ether. A solution of the ether (1·14 g) in CCl_4 (20 ml) was ozonized at 0° for 4 hr. Carbon tetrachloride was removed under vacuum and the residual ozonide was heated with water (20 ml) for 2 hr and extracted with ether. The ether extract was separated into acidic and neutral portions by treatment with KOH. There was very little acidic material. The neutral portion, a yellow oil (1 g), was shown to be a mixture of longihomocamphenilone, longi-isohomocamphenilone and longidione by GLC and TLC analyses and further confirmed by actual isolation via chromatography over alumina.

Lead tetraacetate oxidation of longifolene

Isolation of longihomocamphenilone (VIII), *longidione* (X) *and isolongifolol* (XI). A mixture of longifolene (80 g), glacial acetic acid (400 ml) and lead tetraacetate (250 g) was kept for 2 days in the dark at room temp and then heated on a water bath at 60–70° for 12 hr, when the whole of lead tetraacetate went into solution. The reaction mixture was cooled and alcoholic NaOH solution added slowly until precipitation of $Pb(OH)_2$ which was filtered off. The clear alkaline alcoholic solution was refluxed for 6 hr. The saponified material was worked up in the usual manner and the neutral product (78 g) chromatographed over alumina (gr.II, 2 kg), and eluted with pet. ether (3 l), benzene (2 l.) and ether (2 l.). The pet. ether eluate gave longifolene (35 g). The benzene eluate initially gave longihomocamphenilone (21 g) followed by longidione (3 g). The ether eluate gave the alcohol isolongifolol (XI, 4 g) which was crystallized several times from pet. ether to afford needle shaped flaky crystals; purity was ascertained by GLC and TLC analyses; m.p. 112°, $(\alpha)_D$ −50·4° (*c*, 5·85). IR bands at: 3330, 3000, 1471, 1370, 1220, 1176, 1124, 1081, 1058, 1033, 1010, 1000, 980, 943 and 885 cm^{-1}. (Found: C, 81·39; H, 11·8. $C_{15}H_{26}O$ requires: C, 81·02; H, 11·71%).

Oxidation of isolongifolol (XI) *to isolongifolic acid* (XII) *by Jones' reagent*

A solution of isolongifolol (100 mg) in dry acetone (5 ml) was treated dropwise with Jones' reagent (1 ml) until a pale yellow colour persisted. After keeping at room temp for 15 min, a little methanol was added, followed by water. The product was extracted with ether. The organic acid contained in the ether extract was isolated and finally crystallized from aqueous methanol to yield isolongifolic acid (75 mg), m.p. 136–137°, $(\alpha)_D$ − 11·8° (*c*, 6·1). (Found: C, 76·08; H, 9·87. $C_{15}H_{24}O_2$ requires: C, 76·22; H, 10·24%).