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STUDIES ON SESQUITERPENOIDS—XIX[1]

STRUCTURE AND ABSOLUTE CONFIGURATION OF LIGULOXIDE, LIGULOXIDOL AND LIGULOXIDOL ACETATE[2]

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Abstract—Three closely related sesquiterpene oxides of the guaiane series, named liguloxide (III), liguloxidol (IV) and liguloxidol acetate (V), have been isolated from the aerial parts of *Ligularia fischeri* Turcz. The absolute configuration of these compounds has been clarified on the basis of the correlation of liguloxide (III) with the known guaioxide (XIX) by epimerization of the C-4 methyl group of the latter compound with the aid of microbial hydroxylation at that position.

We previously reported the isolation of ligularone (I),[3] an eremophilane type sesquiterpene, from the aerial parts of *Ligularia fischeri* Turcz (Japanese name: Otakarakō). We have also isolated three new sesquiterpenes of the guaiane series, together with the known furanoeremophilane (II),[4] and named them liguloxide (III), liguloxidol (IV) and liguloxidol acetate (V), respectively.

Distillation of an ether extract of the aerial parts of this plant, followed by repeated column chromatography gave, in order of increasing polarity, furanoeremophilane[4] (0·02% yield from dried material), liguloxide (0·10%), ligularone[3] (0·52%), ligul oxidol (0·08%) and liguloxidol acetate (0·08%).

Liguloxide (III), $C_{15}H_{26}O$, has m.p. 36°, $[\alpha]_D$ $-58\cdot2°$, and on dehydrogenation with Pd-C it gave S-guaiazulene. The IR spectrum of liguloxide shows no hydroxyl or carbonyl absorptions. The NMR spectrum displays two doublets centered at τ 9·13

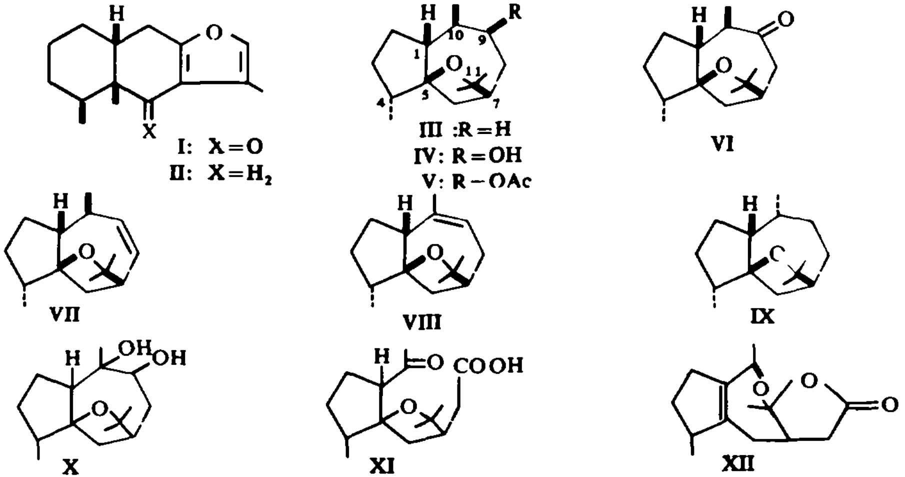


Chart 1

and 9·07 (Me on C-4 and C-10), and also two singlets at τ 8·84 and 8·68 (Me on C-11), but no signals below τ 7·7. This chemical and spectral evidence shows that liduloxide is a guaiane sesquiterpene having a ditertiary ether bridge between C-11 and C-1 or C-5.

Liguloxidol (IV), $C_{15}H_{26}O_2$, a colorless oil, $[\alpha]_D$ −36·8°, exhibits a hydroxyl absorption at 3465 cm^{-1}; when treated with acetyl chloride in pyridine it gave an acetate, which was identical with the naturally occurring liguloxidol acetate (V), $C_{17}H_{28}O_3$, m.p. 85°, $[\alpha]_D$ −52·0°. Jones oxidation of liguloxidol gave a ketone (VI), m.p. 115°, ν_{max} 1702 cm^{-1}, the absorption indicating that the hydroxyl group in liguloxidol is present in the seven-membered ring. Heating liguloxidol with mesyl chloride in pyridine produced a mixture of two dehydrated compounds (VII and VIII), which were separable by preparative GLC. Hydrogenation of VII, which contains a —CH═CH— group (τ 4·67, 2H, m), led to the formation of liguloxide (III), showing that liguloxidol has the same structure as liguloxide except for an additional hydroxyl group. The hydroxyl group should be located at C-9 because the other dehydrated compound (VIII) carries a —CMe═CH— grouping (τ 8·35, 3H). Hydrogenation of VIII afforded a 1 : 1 mixture of liguloxide (III) and 10-epiliguloxide (IX), a colorless oil, $[\alpha]_D$ −3·5°. Since the three natural products are found to possess the same framework, our next concern is to decide the terminal position of the ether bridge in these compounds (C-1 or C-5). This was solved by the following two experiments.

Osmium tetroxide oxidation of 9-dehydroliguloxide (VIII) yielded a 1 : 1 mixture of two *cis*-diols (X), which were successively oxidized with periodic acid and Jones reagent to form a keto-acid (XI), $C_{15}H_{24}O_4$, m.p. 96°. In the NMR spectrum of XI, there appears an active methine signal at τ 6·72 as a triplet (J=9 c/s), the signal pattern being in good agreement with that of the C-17 proton in 3α,12β-diacetoxypregnane-20-one.[5] This suggests that the keto-acid (XI), and thus in turn liguloxide (III), has a hydrogen atom on C-1, i.e. the etereal oxygen in these compounds is linked to C-5.

Acid treatment of the keto-acid (XI) gave a keto-lactone (XII) in 70% yield. This compound shows absorptions at 253 mμ (ε 6640);[6,7] 1765 (γ-lactone), 1672 and 1605 cm^{-1} (αβ-unsaturated ketone); and no signals due to vinyl protons or a vinyl methyl group in its NMR spectrum, thus agreeing with the assigned structure. The formation of XII as a single major product also supports the view that the terminal of the ether bridge in liguloxide is situated on the β-position towards C-10, namely, on C-5.

We initially assigned a wrong stereochemistry to liguloxide, but as our initial reasoning later played an important role in our deriving the correct assignment (see below), we wish to describe first the incorrect conclusion.

In order to determine the absolute configuration of liguloxide, we first examined the acid-catalysed ether-cleavage of the compound to see whether it produces the known guaiol (XIII)[8] or not. Treatment of liguloxide with BF_3 in acetic anhydride in the presence of lithium iodide[9] afforded, after hydrolysis and chromatography on alumina, a mixture of its ether-cleaved compounds showing the same R_f value on TLC as guaiol. GLC inspection of the mixture disclosed several peaks, but none of them corresponded to that of guaiol. We next treated 10-epiliguloxide similarly, and detected in the reaction mixture a compound having the same retention time as guaiol.

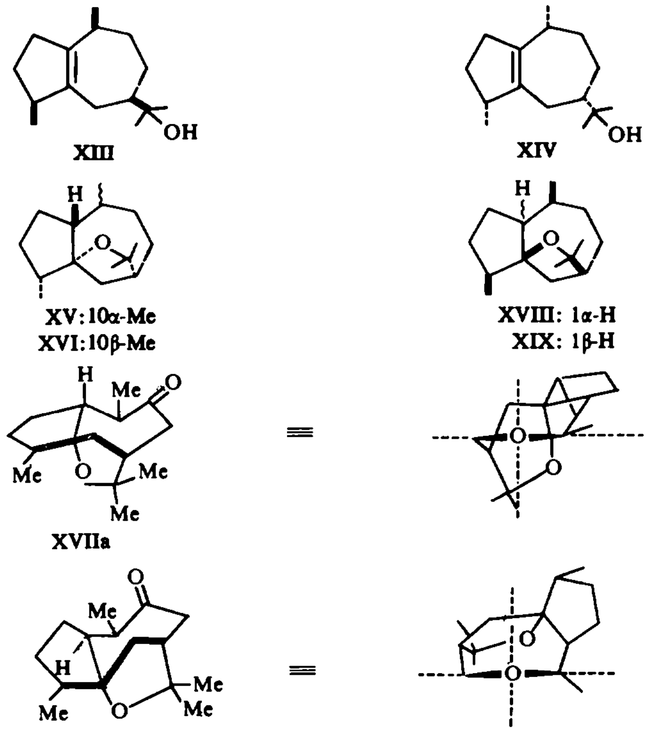


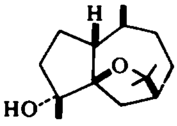
CHART 2

Preparative GLC isolated the compound (XIV) in a crystalline form, $C_{15}H_{26}O$, m.p. 89–90°, $[\alpha]_D$ +28·6° (±2·4°), shown to be the enantiomer of natural (−)-guaiol (XIII), m.p. 89–90°, $[\alpha]_D$ −31·2° (±0·7°), by a comparison of their IR and NMR spectra. From this successful correlation of 10-epiliguloxide with guaiol we deduced that the configuration of the methyl groups at C-4 and C-10 as well as the isopropyl group at C-7 in 10-epiliguloxide were all α as shown in XV, and thus the stereochemistry of liguloxide was considered to be XVI. The β-configuration of hydrogen atom on C-1 was deduced from ORD measurements on 9-oxoliguloxide. Considering that the ketone is stable to alkali, i.e. the methyl group on C-10 is equatorial-like, it could be restricted to two conformations (XVIIa and b), the former carrying 1β-hydrogen while the latter 1α-hydrogen. The ORD measurement of this ketone showed a negative Cotton effect curve (a = −76). Although the negative sign was applicable to both conformers, the amplitude agreed with a value (above 60)[10] expected from XVIIa, and not with a value (below 60)[10] expected from XVIIb.

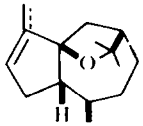
The process for the revision of this assignment is as follows:

At that time the structure of guaioxide, a constituent of guaiac wood oil, was thought to be most likely XVIII.[11] Hence we considered that 10-epiliguloxide must be the antipode of guaioxide. However, comparison of the spectra of these two compounds showed that they are not enantiomorphic, and this prompted us to re-examine the structure of guaioxide. We have studied the structure of this saturated sesquiterpene oxide by the introduction of hydroxyl groups into the molecule with microorganisms, and proposed an alternative structure XIX for the compound.[12] Meanwhile Ehret and Ourisson reported a preparation of 1-epiguaioxide,[13] the structure of which should now be represented by formula XVIII, the former structure for guaioxide. Comparison of the spectra of 10-epiliguloxide and 1-epiguaioxide was carried out by Professor G. Ourisson and it again failed to show their identity. This requires the correction of the stereochemistry of 10-epiliguloxide and thus that of liguloxide itself since the absolute configuration of guaioxide is now confirmed.[12]

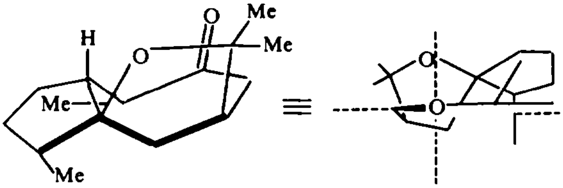
We deduced the stereoformula XVI for liguloxide on the assumption that no inversion would have occurred in the course of transformation of 10-epiliguloxide into (+)-guaiol. Since formula XV is no longer applicable to 10-epiliguloxide, we were forced to consider the possibility that, in the BF_3-reaction, inversion might take place at C-4, the nearest asymmetric center to a terminal of the ether linkage being opened. If this were true, the structure of liguloxide would differ only in the configuration of the ether bridge from the structure of guaioxide (XIX). Because the orientation of the ether bridge cannot be chemically changed, we undertook to prepare various epimers of liguloxide and guaioxide, differing in the configuration at C-1, C-4 and C-10, by microbial hydroxylation at these positions; we should thus be able to correlate liguloxide with guaioxide.



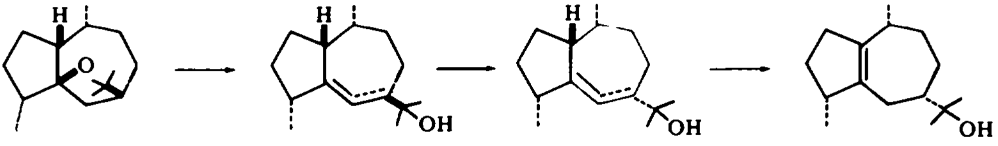
XX



XXI



VIa



IX XXII XXIII XIV

Chart 3

As 4α-hydroxyguaioxide (XX) was already available to us,[12] we first prepared 4-epiguaioxide. Treatment of XX with thionyl chloride in pyridine gave a mixture of dehydrated compounds (XXI), which were catalytically hydrogenated to yield a 2:1 mixture of guaioxide (XIX) and its 4-epimer (III). We found, unexpectedly, that the IR spectrum of the latter compound is identical with that of liguloxide. Also the m.p., $[\alpha]_D$ and retention times of both compounds were comparable, so that liguloxide and 10-epiliguloxide proved to have the stereochemistry shown in III and IX, respectively. Therefore inversion had taken place at C-7 and not at C-4, in the conversion of 10-epiliguloxide (IX) to (+)-guaiol (XIV) (Scheme). The bulky axial isopropyl group at C-7 in XXII would epimerize to the equatorial conformation of XXIII, and then give (+)-guaiol (XIV). Liguloxide and related compounds are thus shown to contain the 7β-isopropyl configuration common to essentially all guaiane-type sesquiterpenes.

The remaining problem is the orientation of the C-9 hydroxyl group in liguloxidol. Examination of the IR spectrum of the compound taken in a dilute solution revealed the presence of strong intramolecular H-bonding between the hydroxyl group and the etheral oxygen atom ($\nu_{max}^{CCl_4}$3472 cm^{-1}), indicating that the hydroxyl group in question has the same β-configuration as the ether bridge. Liguloxidol and liguloxidol acetate consequently have the absolute configurations IV and V, respectively.

Finally, the conformation of 9-oxoliguloxide should be revised from XVIIa to VIa: this is confirmed by ORD measurements showing a negative Cotton curve (a = −76), and by the fact that LAH reduction of the ketone predominantly produced liguloxidol (α-side attack of the reagent).

EXPERIMENTAL

Rotations were taken in $CHCl_3$. NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ with TMS as internal standard with $\tau = 10$. Coupling constants are expressed in c/s. GLC was run using an Aerograph Autoprep model A-700 instrument.

Isolation of liguloxide (III), *liguloxidol* (IV) *and liguloxidol acetate* (V) *from the plant.* Dried leaves and stems of *Ligularia fischeri* Turcz (9·5 kg) were cut into pieces and extracted with ether (40 l × 3) at room temp for 3 days. The combined ether soln was evaporated to leave a dark green residue (398 g). The residue (30·1 g) was distilled to give a yellow oil (10·8 g), b.p. 90–130°/5 mm, which was chromatographed on silica gel (300 g) yielding three fractions: fraction 1, light petroleum (1·782 g); fraction 2, light petroleum–ether (98:2) (4·605 g); fraction 3, light petroleum–ether (95:5, 9:1, 4:1) (4·254 g).

Fraction 1 was rechromatographed on alumina (activity II, 180 g) in light petroleum soln to give hydrocarbons and furanoeremophilane (II, 0·138 g) (identified by the IR spectrum and retention time).

Fraction 2 was dissolved in light petroleum (10 ml) and left in a refrigerator giving ligularone (I) as colorless prisms (1·981 g), m.p. 64° (identified by comparison of IR spectra and the mixed m.p.). The mother liquor was chromatographed on alumina (activity V, 250 g) and eluted with light petroleum. The first eluate gave liguloxide (III) as a colorless oil (0·688 g), which was crystallized from acetone to produce colorless prisms, m.p. 36°, $[\alpha]_D^{23}$ −58·2° (±2°) (*c* 1·034), the spectral data of which are given above. (Found: C, 80·92; H, 11·90. $C_{15}H_{26}O$ requires C, 81·02; H, 11·79%). The second eluate gave crystalline ligularone (I, 1·696 g).

Fraction 3 was rechromatographed on silica gel (400 g) and eluted successively with light petroleum and light petroleum–ether (99:1, 98:2, 95:5, 9:1). The fraction eluted with light petroleum–ether (9:1) furnished a pale yellow oil (1·198 g), which showed two peaks of retention times 9·2 min (50%) and 15·3 min (50%) on GLC (5% diethyleneglycol succinate; 180°; He 200 ml/min). The compound of retention time 9·2 min was liguloxidol (IV), a colorless oil, $[\alpha]_D^{22}$ 36·8° (±2°) (*c* 1·108); IR (film) 3465 cm^{-1} (OH); NMR 9·05 (3H, d, $J = 6·5$) and 8·98 (3H, d, $J = 6$) [Me on C 4 and C 10], 8·78 (3H, s) and 8·50 (3H, s) [two Me on C-11], and 6·37 (1H, m) [H on C-9]. (Found: C, 75·75; H, 10·82. $C_{15}H_{26}O_2$ requires C, 75·58; H, 11·00%). The compound of retention time 15·3 min was liguloxidol acetate (V), colorless prisms, m.p. 85° (from ether-n-pentane), $[\alpha]_D^{22}$ −52·0° (±2°) (*c* 1·058); IR (CCl_4) 1735 and 1240 cm^{-1} (OAc); NMR 9·12 (3H, d, $J = 6$) and 9·05 (3H, d, $J = 6·3$) [Me on C-4 and C-10], 8·82 (3H, s) and 8·70 (3H, s) [two Me on C-11], 7·93 (3H, s) [OAc] and 4·90 (1H, m) [H on C-9]. (Found: C, 72·62; H, 9·95. $C_{17}H_{28}O_3$ requires C, 72·82; H, 10·06%).

Dehydrogenation of liguloxide (III). Liguloxide (III, 200 mg) was heated at 320° with 10% Pd-C (140 mg) under N_2 for 3 min. The reaction mixture was extracted with light petroleum. The extracts obtained from five runs were combined and extracted with 85% H_3PO_4. The H_3PO_4 layer was poured onto ice to regenerate azulene, which was again extracted with light petroleum and chromatographed on alumina (activity II, 10 g). Light petroleum eluted S-guaiazulene (42 mg) as a blue oil, identified by the IR and UV spectra.

TNB adduct: dark violet needles (from EtOH), m.p. 147°. (Found: C, 61·49; H, 4·99; N, 10·07. $C_{15}H_{18}\cdot C_6H_3O_6N_3$ requires C, 61·31; H, 5·15; N, 10·21%).

Acetylation of liguloxidol (IV). Acetyl chloride (1 ml) was added to a soln of IV (366 mg) in pyridine (5 ml) in an ice-bath and the mixture was left at room temp for 42 hr. Working up in the usual way and crystallization from ether–light petroleum gave liguloxidol acetate (V) as prisms, m.p. 85° (identified by the IR spectrum and mixed m.p.).

Jones oxidation of liguloxidol (IV). Jones reagent (0·6 ml) was added to a soln of IV (500 mg) in acetone (5 ml) in an ice-bath and the mixture was stirred at room temp for 5 min. The reaction mixture was poured into ice-water and extracted to give 9-oxoliguloxide (VI) as colorless prisms (from ether-light petroleum, 385 mg), m.p. 115°, $[\alpha]_D^{28\cdot5}$ $-50\cdot7°$ ($\pm 2°$) (*c* 0·874); IR ($CHCl_3$) 1702 cm^{-1} (cycloheptanone); NMR 9·03 (3H, d, $J=6\cdot5$) and 8·99 (3H, d, $J=6$) [Me on C-4 and C-10], 8·82 (3H, s) and 8·75 (3H, s) [two Me on C-11]; ORD $[\alpha]_{450}$ $-90°$, $[\alpha]_{310}$ $-1493°$, $[\alpha]_{267}$ $+1845°$, $[\alpha]_{250}$ $+1530°$ (*c* 0·670, MeOH). (Found: C, 76·50; H, 10·40. $C_{15}H_{24}O_2$ requires C, 76·22; H, 10·24%).

LAH *reduction of* 9-*oxoliguloxide* (VI). A soln of VI (750 mg) in dry ether (10 ml) was added portionwise to a suspension of LAH (400 mg) in dry ether (5 ml) and the mixture was stirred at room temp for 1 hr. Excess of the reagent was decomposed by addition of water and the mixture was extracted with ether. The ether soln was washed, dried (Na_2SO_4) and evaporated to give a product. The product was purified by chromatography to yield liguloxidol (IV) as a colorless oil (680 mg) (IR spectrum and retention time).

Dehydration of liguloxidol (IV). Mesyl chloride (1 ml) was added to a soln of IV (680 mg) in pyridine (5 ml) in an ice-bath and the mixture was heated at 80° for 5 hr. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The brown extract (598 mg) was purified by chromatography on alumina (activity III, 15 g) to give a pale yellow oil (562 mg), which showed two peaks of retention times 32·2 min (25%) and 39·2 min (75%) on GLC (5% diethyleneglycol succinate; 160°; He 100 ml/min). The compound of retention time 32·2 min was 8-dehydroliguloxide (VII), a colorless oil, IR (film) 1658, 1405 and 690 cm^{-1} (—CH=CH—(*cis*)); NMR 9·08 (3H, d, $J=6\cdot6$) and 9·00 (3H, d, $J=6\cdot5$) [Me on C-4 and C-10], 8·82 (3H, s) and 8·80 (3H, s) [two Me on C-11], and 4·67 (2H, m) [H on C-8 and C-9]. (Found: C, 81·78; H, 11·00. $C_{15}H_{24}O$ requires C, 81·76; H, 10·98%). The compound of retention time 39·2 min was 9-dehydroliguloxide (VIII), a colorless oil, IR (film) 1672 and 823 cm^{-1} (—CH=C$<$); NMR 9·07 (3H, d, $J=6$) [Me on C-4], 8·80 (3H, s) and 8·74 (3H, s) [two Me on C-11], 8·35 (3H, d, $J = 1\cdot5$) [Me on C-10], and 4·80 (1H, m) [H on C-9]. (Found: C, 81·42; H, 11·07. $C_{15}H_{24}O$ requires C, 81·76; H, 10·98%).

Hydrogenation of 8-*dehydroliguloxide* (VII). A mixture of VII (40 mg) and Adams' catalyst (20 mg) in MeOH (10 ml) was hydrogenated at room temp. When 1·1 mol H_2 had been absorbed, the reaction stopped, and the catalyst and solvent were removed. The residue was purified by chromatography on alumina to give a crystalline substance (38 mg), which was sublimated to furnish pure liguloxide (III), m.p. 36° (identified by the IR spectrum and mixed m.p.).

Hydrogenation of 9-*dehydroliguloxide* (VIII). A mixture of VIII (200 mg) and Adams' catalyst (100 mg) in AcOH (10 ml) was hydrogenated at room temp. After uptake of 1·2 mol H_2, the absorption ceased. Filtration of the catalyst and removal of the solvent gave a colorless oil (198 mg). The oil showed two peaks of retention times 11·5 min (50%) and 13·6 min (50%) on GLC (5% diethyleneglycol succinate; 140°; He 100 ml/min). The compound of retention time 11·5 min was liguloxide (III), identified by the IR spectrum and retention time. The compound of retention time 13·6 min was 10-epiliguloxide (IX), a colorless oil, $[\alpha]_D^{24}$ $-3\cdot5°$ ($\pm 0\cdot3°$) (*c* 0·980), NMR 9·15 (3H, d, $J=6$) and 9·10 (3H, d, $J=6\cdot5$) [Me on C-4 and C-10], 8·79 (3H, s) and 8·67 (3H, s) [two Me on C-11]. (Found: C, 81·18; H, 11·79. $C_{15}H_{26}O$ requires C, 81·02; H, 11·79%).

Conversion of 9-*dehydroliguloxide* (VIII) *into the keto-acid* (XI). A soln of OsO_4 (1 g) in dry benzene (4 ml) was added to a soln of VIII (730 mg) in dry benzene (6ml) and dry pyridine (2 ml) in an ice-bath, and the mixture was left at room temp for 5 days. The reaction mixture was saturated with H_2S and the black ppt was filtered off. The filtrate was evaporated *in vacuo* to give a crystalline substance (X, 830 mg), which was shown to be a 1 : 1 mixture of two compounds on TLC (silica gel G; EtOAc; R_f 0·6 and 0·7).

To a soln of X (830 mg) in MeOH (30 ml), a soln of $HIO_4\cdot 2H_2O$ (850 mg) in water (10 ml) was added, and the mixture was left overnight at room temp. Water (10 ml) was added to the reaction mixture, which was concentrated and extracted with $CHCl_3$. The extract was washed with dil

$NaHCO_3$aq and water, dried (Na_2SO_4) and evaporated leaving a crude aldehyde (785 mg), IR (film) 2750. 1725 (CHO) and 1705 cm^{-1} ($COCH_3$). To a soln of the crude product (282 mg) in acetone (4 ml), Jones reagent (0·5 ml) was added in an ice-bath with stirring, and the mixture was stirred at room temp for a further 5 min. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried (Na_2SO_4) and evaporated to yield a crystalline residue, which was recrystallized from ether–light petroleum giving the keto-acid (XI) as colorless plates (198 mg), m.p. 96°, $[\alpha]_D^{24}$ +103·5° (±5·5°) (*c* 0·916); IR (Nujol) 2500–3500, 1728 (COOH) and 1698 cm^{-1} ($COCH_3$); NMR 9·02 (3H, d, $J=6$) [Me on C-4], 9·03 (3H, s) and 8·70 (3H, s) [two Me on C-11], 7·77 (3H, s) [Me on C-10], 6·72 (1H, t, $J=9$) [H on C-1] and 0·87 (1H, broad) [COOH]. (Found: C, 66·91; H, 9·04. $C_{15}H_{24}O_4$ requires C, 67·13; H, 9·02%).

Acid treatment of the keto-acid (XI). To a soln of XI (200 mg) in MeOH (7·5 ml), 50% H_2SO_4 (2·5 ml) was added dropwise and the mixture was left at room temp for 1 day. Water (10 ml) was added to the mixture, which was concentrated and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated leaving a residue (195 mg). The residue was dissolved in light petroleum and chromatographed on silica gel (10 g). Elution with light petroleum–ether (9 : 1) gave the methyl ester of XI as a colorless oil (65 mg), IR (film) 1738 (COOMe) and 1703 cm^{-1} (COMe); NMR 9·03 (3H, d, $J=6$) [Me on C-4], 9·07 (3H, s) and 8·72 (3H, s) [two Me on C-11], 7·79 (3H, s) [Me on C-10], 6·73 (1H, t, $J=9$) [H on C-1] and 6·32 (3H, s) [COOMe]. This was identical with an authentic sample prepared by methylation of XI with CH_2N_2 (IR spectrum).

Elution with light petroleum–ether (4 : 1) yielded the keto-lactone (XII) as a colorless oil (92 mg), UV λ_{max} 253 mμ (ε 6640) (EtOH); IR (film) 1765 (γ-lactone), 1672 and 1605 cm^{-1} (αβ-unsaturated ketone); NMR 8·81 (3H, d, $J=7$) [Me on C-4], 8·70 (3H, s) and 8·48 (3H, s) [two Me on C-11], and 7·80 (3H, s) [Me on C-10]. Semicarbazone of XII: m.p. 188–189°, $[\alpha]_D^{24}$ +67·5° (±1·2°) (*c* 0·852). (Found: C, 62·25; H, 8·16; N, 13·69. $C_{16}H_{25}O_3N_3$ requires C, 62·52; H, 8·20; N, 13·67%).

BF_3-*Treatment of liguloxide* (III). To a soln of III (1 g) and LiI (500 mg) in Ac_2O (10 ml), BF_3–Et_2O (0·4 ml) was added in an ice-bath and the mixture was left at 0° for 2 days. The reaction mixture was poured onto ice-water and extracted with ether. The ether soln was washed with 5% Na_2CO_3aq and water, dried (Na_2SO_4), and evaporated leaving a brown oil (996 mg), which was chromatographed on silica gel (40 g). Elution with light petroleum gave hydrocarbons (234 mg). Successive elution with light petroleum–ether (95 : 5) furnished, after removal of the solvent, a yellow oil (720 mg). The oil was hydrolysed with 5% MeOH–KOH (10 ml) under reflux for 2 hr. The reaction mixture was concentrated, diluted with water and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated to leave a residue (648 mg), which was chromatographed on alumina (activity IV, 30 g). Elution with light petroleum recovered liguloxide (III, 483 mg) unchanged (identified by the IR spectrum). Elution with light petroleum–ether (9 : 1) gave an oil (OH fraction), which showed five peaks of retention times 8·5 min (5%), 9·2 min (33%), 10·9 min (6%), 12·2 min (48%) and 14·2 min (8%) on GLC (5% phenyldiethanolamine succinate; 170°; He 200 ml/min). Under the condition, guaiol (XIII) showed retention time 8·8 min.

BF_3-*Treatment of* 10-*epiliguloxide* (IX). BF_3-Et_2O (0·3 ml) was added to a cooled soln of IX (465 mg) and LiI (230 mg) in Ac_2O (10 ml), and the mixture was left at 0° for 1 day. The reaction mixture was poured onto ice-water and extracted with ether. The extract was washed with 5% Na_2CO_3aq and water, dried (Na_2SO_4) and evaporated to give a brown oil (494 mg), which was chromatographed on silica gel (50 g). Elution with light petroleum gave hydrocarbons (108 mg). Successive elution with light petroleum–ether (98 : 2) afforded an oil (350 mg), which was hydrolysed as described above giving a product (335 mg). This was chromatographed on alumina (activity IV, 15 g), and elution with light petroleum recovered 10-epiliguloxide (286 mg) unchanged (identified by the IR spectrum). Elution with light petroleum–ether (9 : 1) gave an oil (OH fraction), which showed six peaks of retention times 8·8 min (25%), 9·7 min (22%), 10·9 min (10%), 11·1 min (17%), 11·7 min (20%) and 13·1 min (6%) on GLC (5% phenyldiethanolamine succinate; 170°; He 200 ml/min). The compound of retention time 8·8 min was (+)-guaiol (XIV), m.p. 89–90°, $[\alpha]_D^{24}$ +28·6° (±2·4°) (*c* 0·270), IR (CS_2) 3620 and 3400 cm^{-1} (OH); NMR 9·04 (3H, d, $J=7$) and 9·00 (3H, d, $J=7$) [Me on C-4 and C-10], and 8·83 (6H, s) [two Me on C-11]. (Found: C, 81·12; H, 11·77. $C_{15}H_{26}O$ requires C, 81·02; H, 11·79%).

Preparation of liguloxide (III) *from 4α-hydroxyguaioxide* (XX). To a cooled soln of XX (220 mg) in pyridine (2 ml), thionyl chloride (0·2 ml) was added and the mixture was left at room temp for 5 min. Working up in the usual manner gave a mixture of two dehydrated compounds (XXI) as an oil (175 mg). A mixture of XXI (86 mg) and Adams' catalyst (20 mg) in AcOH (10 ml) was hydrogenated at room temp. When 1 mol H_2 had been absorbed, the reaction stopped. After removal of the catalyst and solvent, the residue (90 mg) was chromatographed on alumina (activity II, 20 g) and eluted with light petroleum. The head eluate gave guaioxide (XIX) as a colorless oil (49 mg), identified by the IR spectrum and retention time. The tail eluate furnished liguloxide (III) as colorless prisms (sublimation, 28 mg), m.p. 36° (IR spectrum and mixed m.p.).

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REFERENCES

[1] Part XVIII. H. Minato and I. Horibe, *J. Chem. Soc.* (C), 2131 (1968)

[2] Preliminary communications: H. Ishii, T. Tozyo and H. Minato, *Chem. Commun.* **106**, 1534 (1968)

[3] H. Ishii, T. Tozyo and H. Minato, *Tetrahedron* **21**, 2065 (1965)

[4] H. Ishii, T. Tozyo and H. Minato, *J. Chem. Soc.* (C), 1545 (1966)

[5] Varian Associates, *High Resolution NMR spectra Catalog*, No. 361, Palo Alto, California (1962)

[6] W. M. Schubert and W. A. Sweeney, *J. Am. Chem. Soc.* **77**, 2297 (1955)

[7] H. Hikino, K. Meguro, Y. Sakurai and T. Takemoto, *Chem. Pharm. Bull.* (*Japan*) **14**, 1241 (1966)

[8] K. Takeda and H. Minato, *Ibid.* **9**, 619 (1961); H. Minato, *Ibid.* **9**, 625 (1961); H. Minato, *Tetrahedron* **18**, 365 (1962)

[9] R. D. Youssefyeh and Y. Mazur, *Tetrahedron Letters*, 1287 (1962)

[10] C. Beard, C. Djerassi, J. Sicher, F. Sipos and M. Tichy, *Tetrahedron* **19**, 919 (1963)

[11] R. B. Bates and R. C. Slagel, *Chem. & Ind.*, 1715 (1962); P. Ledoux, B. P. Vaterlaus and G. Chiurdoglu, *Bull. Soc. chim. belges* **75**, 551 (1966)

[12] H. Ishii, T. Tozyo, M. Nakamura and H. Minato, *Tetrahedron* **26**, (1970)

[13] C. Ehret and G. Ourisson, *Bull. Soc. chim. Fr.* 2629 (1968)