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IRCININ-1 AND -2, LINEAR SESTERTERPENES FROM THE MARINE SPONGE *IRCINIA OROS*

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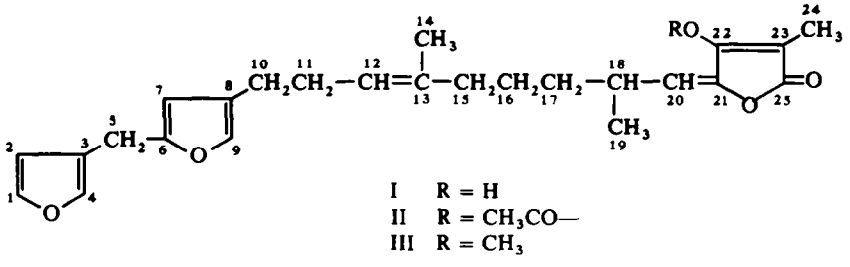
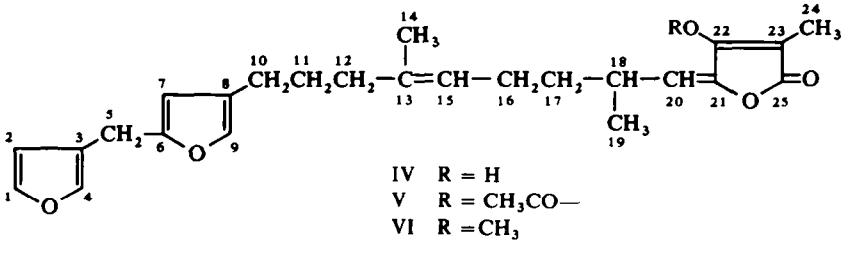
Abstract—Two isomeric linear difurano sesterterpenes, ircinin-1 and -2, have been identified in the sponge *Ircinia oros*.

IN OUR STUDIES on the metabolites of Porifera, we have isolated a number of related C-21 furanoterpenes,[1] apparently oxidized sesterterpenes, from *Spongia nitens*, *officinalis* and *Hippospongia communis*. We now report the occurrence of two sesterterpenes, ircinin-1 (I) and ircinin-2 (IV), in the sponge *Ircinia oros*.



I R = H
II R = CH_3CO—
III R = CH_3



IV R = H
V R = CH_3CO—
VI R = CH_3

From the methanolic extracts of the fresh tissues we have isolated an oily Ehrlich positive and $FeCl_3$ positive substance, $C_{25}H_{30}O$. (mass spectrum and elemental analysis), resistant to all attempts at separation. Spectroscopic evidence suggests the presence of an enol (λ_{max}(MeOH) 260 nm (ε 12,500); λ_{max}(MeOH/OH^-) 248 and 310 (ε 10,500 and 7,500)) and an α,β-unsaturated γ-lactone (ν_{max}($CHCl_3$) 3150 (b), 1735, and 1635 cm^{-1}) functions probably forming together a conjugated tetronic acid.[2]

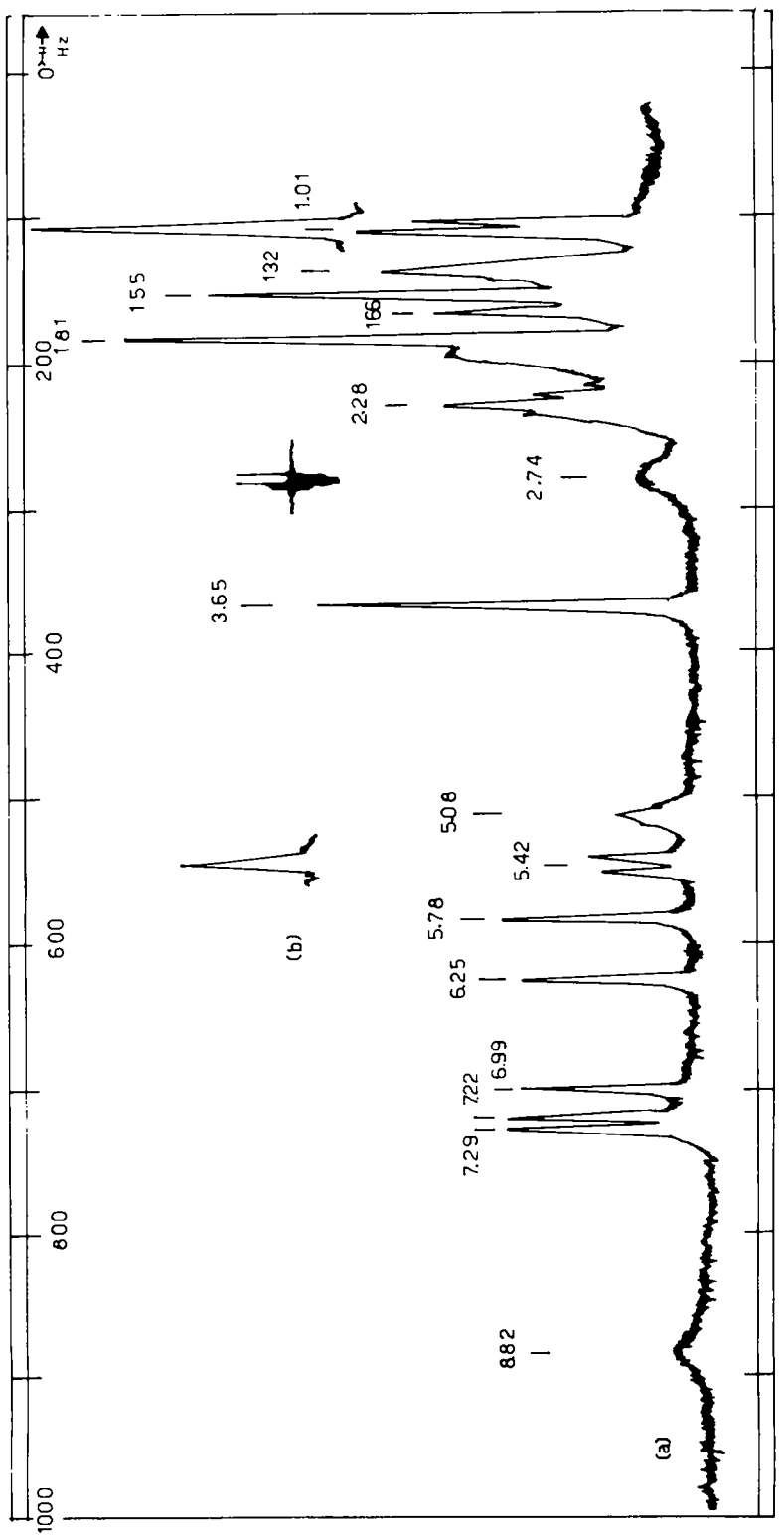


FIG 1a. 100 MHz NMR spectrum (CCl_4) of the mixture of ircinin-1 (I) and -2 (IV)

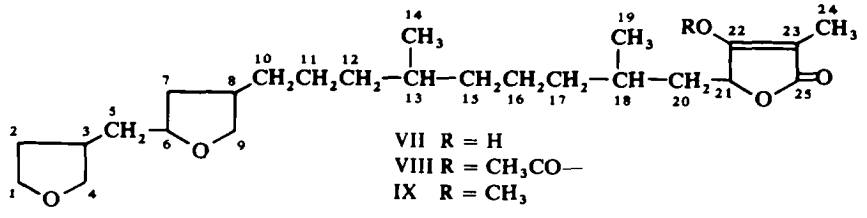
FIG 1b. Decoupling experiment by irradiation at δ 2·74 (H-C-18)

The NMR spectrum (Fig. 1) supports this view (a broad signal at δ 8·82 (1H) exchangeable with D_2O (OH), and a 3H singlet at δ 1·81 (Me on C-23) (1 formulae I and IV), and shows the presence of two furan rings [5 broad 1H singlets at δ 7·29, 7·22 and 6·99 (α-furano protons) and at δ 6·25 and 5·78 (β-furano protons)] linked to each other by a methylene group (2H broad singlet at δ 3·65; irradiation on this signal sharpens all five furano proton singlets). Further PMDR experiments established that the mono-substituted furan ring is β-substituted; irradiation on the δ 6·25 (H-2; formulae I and IV) signal causes a sharpening of two of the α-furano proton signals at δ 7·29 and 7·22; in the reverse experiment, irradiation at either δ 7·29 or 7·22 resulted in a distinct sharpening of the broad singlet at δ 6·25. Biogenetic considerations (isoprene rule) suggests that the furan rings are linked to each other and to the chain as shown in I and IV. Furthermore PMDR and PMTR experiments show the presence in the molecule of the partial structure $-CH_2-CH(Me)-CH=C<$

[δ 5·42 (1H, d, J = 9 Hz, CH=C), 2·74 (1H, bm, —C<u>H</u>(Me)—) and 1·01 (3H, d, J = 7 Hz, —CH(C<u>H</u>$_3$)]. Irradiation at δ 2·74 collapses both doublets at δ 5·42 and 1·01 to singlets (Fig. 1). Simultaneous irradiation at δ 5·42 and 1·01 converts the broad methine multiplet at δ 2·74 into a triplet (J = 7 Hz). To confirm these assignments we simultaneously irradiated the Me doublet at δ 1·01 and the complex signal at δ 1·32 and so collapsed the methine multiplet to a doublet (J = 9 Hz). The partial structure $-CH_2CH(Me)-CH=C<$ is very probably conjugated with the tetronic acid residue as the olefinic proton resonance is shifted upfield on acetylation (to δ 4·84).

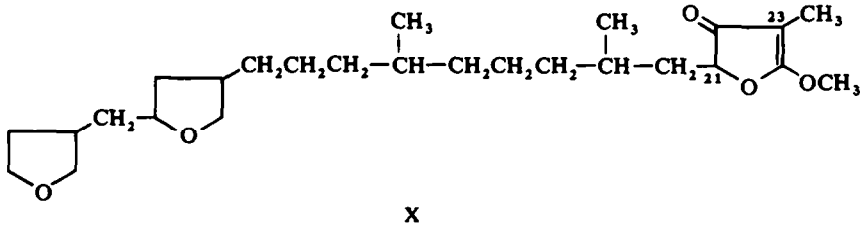
Finally in the NMR spectrum of the natural substance we could observe a further olefinic proton resonance (δ 5·08 m) and two singlets at δ 1·55 and 1·66 (Me—C=C), integrating together for 3H. This suggests that the natural product under investigation is very probably a mixture of two isomers differing either in the configuration (*cis* or *trans*) or in the position of this double bond as shown in I and IV. In agreement with the observation that the natural substance is a mixture of two components, the acetylation product (mixture of II and V) M^+ 452, ν_{max} 1770 ($>C=O$, enolacetate), 1750 and 1650 cm^{-1}, δ CH_3CO_2—2·28 (3H, s), could be resolved by GLC (2·5% SE-30, temp. 280°; glass column): two peaks with very similar retention times were observed, the peak areas being in the same ratio as that of the two vinyl methyl NMR signals.

Hydrogenation (Pd/C in MeOH, 80 Atm, 80°) of the mixture of the two natural isomers I and IV gave a single dodecahydro derivative (VII), $C_{25}H_{42}O_5$ (M^+ 422)

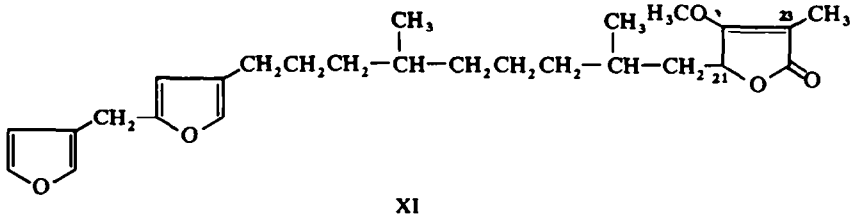


VII R = H
VIII R = CH_3CO—
IX R = CH_3

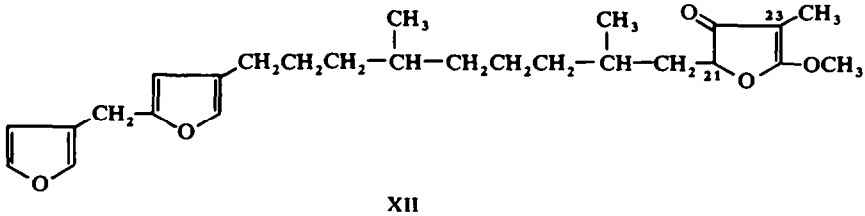
(apart from stereoisomers), the NMR spectrum of which contained a new Me doublet at δ 0·84, the signals at δ 1·55 and 1·66 having disappeared. No signal due to an olefinic proton was observed in the NMR spectrum of VII and the UV [λ_{max}(MeOH) 230 and 258 nm (ε 7,320 and 6,490); λ_{max}(MeOH/H^+) 230 (ε 9,060) nm; λ_{max}(MeOH/OH^-) 258 nm (ε 14,600)] and IR [($CHCl_3$) 3100 and 2710 (OH, enol) and 1760 (w), 1735 (m) and 1660 (s) cm^{-1}; (ether) 1760 (s) and 1670 (m) cm^{-1}] spectra are fully consistent with the presence of a tetronic acid residue[2] in the molecule, which must carry a Me group on C-23 (3H singlet at δ 1·72). On acetylation with Ac_2O-pyridine VII gave a single *acetate* (VIII) M^+ 464, ν_{max}(liquid film) 1775, 1760, 1690 and 1170 cm^{-1}, and, as expected, on methylation with CH_2N_2 afforded two isomeric O-methyl derivatives,[3] (IX) M^+ 436, singlet peak in GLC [λ_{max}(MeOH) 230 nm (ε 10,200), ν_{max} (liquid film) 1755, 1670 and 1050 cm^{-1}; δ vinyl Me 2·07][3] and (X), M^+ 426, single peak in GLC [λ_{max}(MeOH) 263 nm (δ 9,300); ν_{max}(liquid film) 1760 (w), 1700 (w), 1670 (w), 1610 (s) and 1150 (m); δ vinyl Me 1·51].[3] It was also possible to obtain a single tetrahydroderivative (apart from stereoisomers) by hydrogenation in pyridine (Pd/C, 80 Atm, 80°) of the mixture of the two isomers I and IV. This, on methylation with CH_2N_2, behaved similarly to VII giving two isomeric O-methyl derivatives, all the spectral data of which (MS, NMR, IR and UV; experimental) are fully consistent with structures XI and XII respectively. Furthermore, as in the case of the dodecahydro



X



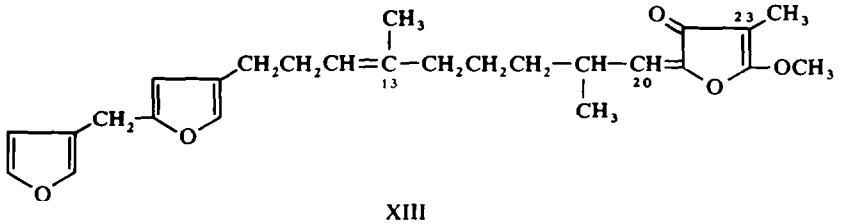
XI



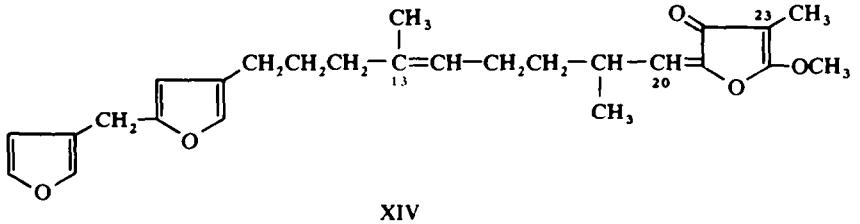
XII

and tetrahydro derivatives, the natural mixture of I and IV, containing a conjugated tetronic acid residue, when treated with CH_2N_2, afforded two mixtures of O-methyl

derivatives, a mixture of III and VI which was more abundant and resolvable on GLC (2·5% SE-30, temp. 280°, glass column) and a mixture of XIII and XIV in minor quantity. All the spectral data of both mixtures, (experimental), support the above structures.



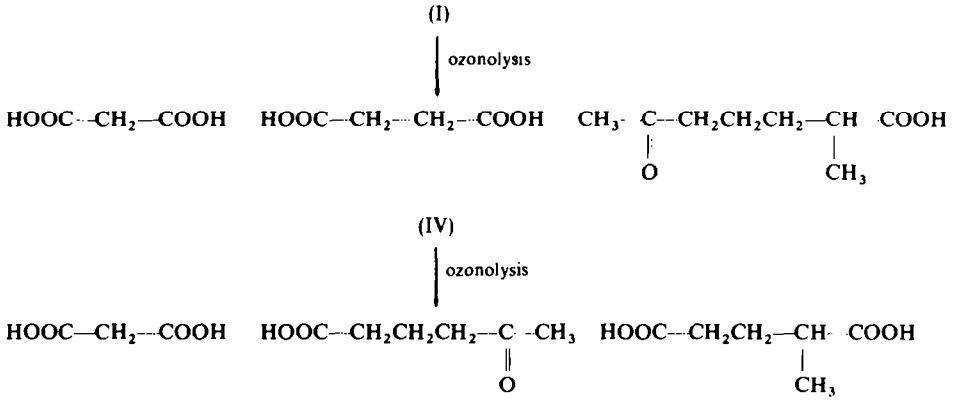
XIII



XIV

Oxidative ozonolysis of the mixture of natural compounds gave malonic, succinic, 2-methyl-6-oxoeptanoic, 5-oxohexanoic and 2-methylglutaric acids (Scheme 1). This

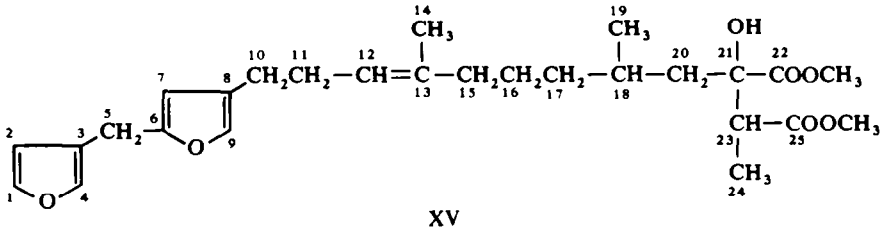
SCHEME 1



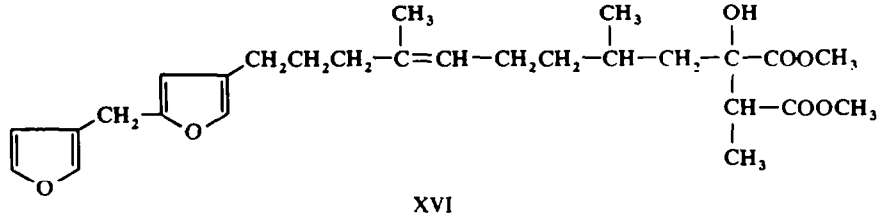
confirms that the two isomers differ in the position of the central double bond, and establishes the structures I, (ircinin-1) and IV, (ircinin-2), for these new sesterterpenes.

Another piece of evidence in favour of the presence of the conjugated tetronic acid moiety in I and IV came from treatment of the mixture of the two compounds with hot concentrated aqueous alkali and subsequent esterification with CH_2N_2 which gave, as main transformation products, a mixture of XV and XVI resistent to all

attempts at separation; M^+ 474, ν_{max}(liquid film) 3500 (OH), 1730 (CO, ester) cm^{-1};



XV



XVI

λ_{max}(MeOH) 220 nm (ε 11,000; furan chromophore). The NMR spectrum revealed two OMe peaks overlapping with the C_4H_3O—$\underline{CH_2}C_4H_2O$ (δ 3·72, 3·68 and 3·65) signal, and a sec-Me resonance at lower field (δ 1·14, J = 6 Hz, Me on C-23), which collapse to a singlet on irradiation at δ 2·7 (—CH—CO_2Me). In the NMR spectrum of the mixture of these two dicarboxylic esters, two singlets at δ 1·54 and 1·64 (CH_3—C=C) are still present. The formation of XV and XVI is explained by hydrolysis of the lactone rings of I and IV and subsequent benzilic rearrangement of the α-diketones so formed.[4]

The occurrence of linear sesterterpenes in these sponges supports the biogenetic hypothesis that the C-21 furanoterpenes previously reported,[1] are degraded sesterterpenes. With the isolation of ircinin-1 and -2, six sesterterpenes are now known.[5]

EXPERIMENTAL

Instrumental techniques were given in the previous papers.[1] Column chromatography was performed with Merck 0·05–0·2 mm silica gel, and TLC with Merck F 254.

Isolation of the mixture of ircinin-1 (I) *and* -2 (IV) *from* Ircinia oros. Sponges (*Ircinia oros*) collected in the Bay of Naples, were obtained from the supply department of the Zoological Station (Naples). The fresh material (160 g dry weight after extraction) was extracted three times with MeOH for three days; the combined extracts (4 l) were concentrated in *vacuo* and the remaining aqueous solution extracted with ether (1·5 l in 3 portions). After evaporation of solvent a brown oil (6·5 g) was obtained, which was chromatographed on silica gel (300 g). A mixture of ircinin-1 (I) and -2 (IV) migrated out after 7·2 l (3 g) when the column was washed with C_6H_6 (4 l) followed by C_6H_6-ether (9 : 1). The mixture of the two isomers, resistant to separation (TLC on SiO_2 and Al_2O_3 with and without $AgNO_3$), showed the following spectral data: λ_{max} (MeOH) 260 nm (ε 12,500), λ_{max}(MeOH/OH^-) 248 and 310 nm (ε 10·500 and 7,500); ν_{max} ($CHCl_3$) 3150 (b, OH), 1735 (>CO, α,β-unsaturated γ-lactone), 1635 (>C=C<) cm^{-1}; NMR (CCl_4) (Fig. 1); MS *m/e* (%) 310 (50, M^+), 395 (3, M^+—CH_3), 329 (15, M^+—$C_4H_3OCH_2$), 215 (95), 175 (15), 162 (100), 135 (10), 81 (30, $C_4H_3OCH_2^+$) and 67 (20, $C_4H_3O^+$). (Found: C, 72·98; H, 7·45. $C_{25}H_{30}O_5$ requires C, 73·15, H, 7·73%).

Acetylation of the mixture of ircinin-1 (I) *and* -2 (IV). On acetylation with Ac_2O and pyridine at reflux for 20 min the natural mixture of I and IV (120 mg) afforded an oil, purified by prep. TLC (C_6H_6; R_f = 0·3) to give 80 mg of *acetate* (mixture of two isomers II and V) (M^+ 452): λ_{max} (C_6H_{12}) 222 and 265 nm, (ε 9,400 and 13,100): ν_{max} ($CHCl_3$) 1770 (>C=O, acetate) 1750 (>C=O, α,β-unsaturated γ-lactone) 1650 (>C=C<) 1170 and 1135 cm^{-1}; NMR (CCl_4) 4·84 (1H, d, J = 9 Hz, H-C-20), 2·28 (3H, s, CH_3—CO—), 1·78 (3H, s, Me on C-23). (Found: C, 72·03; H, 7·14. $C_{27}H_{32}O_6$ requires: C, 71·66; H, 7·13%). By GLC (2·5% SE-30; temp 280°; 2mt, long glass column; carrier gas at a flow of 35 ml/min) the acetylation product gave two peaks with very similar retention times (113 and 130 sec, respectively).

Methylation with diazomethane of the mixture of ircinin-1 (I) *and* -2 (IV). To a soln of 200 mg of the natural mixture of I and IV in MeOH excess of ethereal CH_2N_2 was added. After 10 min the solvent was removed by evapn under red. press. and the oily residue chromatographed on prep. TLC with C_6H_6-ether, 9:1, as eluent. The two bands R_f 0·7 and 0·3, visible in UV light, were scraped off and eluted with $CHCl_3$ to yield the compounds A (120 mg) and B (40 mg).

Compound A (mixture of III and VI): λ_{max} (C_6H_{12}) 216 and 269 nm (ε 9,400 and 9,200); ν_{max} ((iquid film) 1760 (>C=O, α,β-unsaturated γ-lactone), 1640 (>C=C<) and 1550, 1500, 1145, 1065, 1020, 875 and 775 (furan rings)[6,7] cm^{-1}; NMR (CCl_4) δ 5·03 (1H, d, J = 9 Hz, H-C-20), 4·06 (3H, s, OMe), 2·00 (3H, s, Me on C-23), 1·65 and 1·53 (each s, integrating together for 3H, Me on C-13); MS *m/e* (%) 424 (60, M^+), 215 (100), 175 (15), 167 (30), 162 (60), 161 (20) and 81 (30, $C_4H_3OCH_2^+$). (Found: C, 73·95; H, 7·72. $C_{26}H_{32}O_5$ requires C, 73·56; H, 7·60%). GLC (2·5% SE-30; temp. 280°; 2 mt. long glass column; carrier gas at a flow of 35 ml/min) of compound A gave two peaks with very similar retention times (120 and 134 sec., respectively).

Compound B (mixture of XIII and XIV): M^+ 424; λ_{max} (MeOH) 209, 247 and 315 nm (ε 8,500, 8,500 and 3,700); ν_{max} (liquid film) 1760 (w), 1610 (s) and 1550, 1500, 1145, 1020, 875, 760 (furan rings)[6,7] cm^{-1}; NMR (CCl_4) δ 5·60 (1H, d, J = 9 Hz, H-C-20), 4·04 (3H, s, OMe), 1·57 (3H, s, Me on C-23), 1·63 and 1·53 (each s, integrating together for 3H, Me on C-13). (Found: C, 73·85; H, 7·75. $C_{26}H_{32}O_5$ requires: C, 73·56; H, 7·60%).

Hydrogenation of the mixture of ircinin-1 (I) *and* -2 (IV): *dodecahydroderivative* (VII). The natural mixture of (I) and IV (250 mg) in MeOH (50 ml) was hydrogenated with 25 mg 10% Pd/C as a catalyst at 80° and 80 Atm for 5 hr. Filtn, evap. and prep' TLC (ether/C_6H_6, 9:1, two stages; R_f 0·3) gave VII (150 mg), M^+ 422. λ_{max} (MeOH) 230 and 258 nm (ε 7,320 and 6,420), λ_{max} ($MeOH/H^+$) 230 nm (ε 9,600), λ_{max} ($MeOH(OH^-)$ 258 nm (ε 14,600); ν_{max} ($CHCl_3$) 3100 and 2710 (OH, enol), 1760 (w), 1735 (m) and 1660 (s) cm^{-1}; NMR ($CDCl_3$) δ 4·76 (1H, m, H-C-21), 3·89–3·43 (7H, complex signal, THF α-H), 1·72 (3H, s, Me on C-23), 0·94 (3H, d, J = 6 Hz, *sec*-Me), 0·84 (3H, d, J = 6 Hz, *sec*-Me). (Found: C, 71·21; H, 9·88. $C_{25}H_{42}O_5$ requires C, 71·05; H, 10·02%).

Acetate (VIII): 40 mg of VII were treated with Ac_2O and pyridine at reflux for 20 min. Working up as usual and prep. TLC with C_6H_6/ether, 6:4, as eluent gave VIII, M^+ 464, λ_{max}(MeOH) 216 nm (ε 11,600); ν_{max} (liquid film) 1775 (>CO, acetate), 1760, 1690 and 1170 cm^{-1}; NMR (CCl_4) δ 5·08 (1H, m, H-C-21), 2·25 (3H, s, CH_3CO—), 1·72 (3H, s, Me on C-23).

O-*Methyl derivatives* IX *and* X. 100 mg VII in MeOH were treated with excess CH_2N_2 in ether. By prep. TLC with C_6H_6/ether, 1:1, as eluent, the lactone (IX) (31 mg; R_f 0·4) and the ketone X (29 mg; R_f 0·3) were isolated.

IX (single peak in GLC; 2·5% SE-30 at 220°), M^+ 436: λ_{max}(MeOH) 230 nm (ε 10,200); ν_{max}(liquid film) 1755, 1670, and 1060 cm^{-1}; NMR (CCl_4) δ 4·48 (1H, m, H-C-21), 4·06 (3H, s, OMe), 2·07 (3H, s, Me on C-23).

X (single peak in GLC; 2·5% SE-30 at 220°), M^+ 436: λ_{max}(MeOH) 263 nm (ε 9,300); ν_{max} (liquid film) 1760 (w), 1700 (w), 1670 (w), 1610 (s) and 1150 (m) cm^{-1}; NMR (CCl_4) δ 4·44 (1H, m, H-C-21), 3·88 (3H, s, OMe), 1·51 (3H, s, Me on C-23).

Hydrogenation of the natural mixture of ircinin-1 (I) *and* -2 (IV) *and subsequent* CH_2H_2 *methylation*: *tetrahydroderivatives* XI *and* XII. The natural mixture of I and IV (200 mg) in EtOH (30 ml) and pyridine (4 ml) was hydrogenated with 30 mg 10% Pd/C as a catalyst at 80° and 80 Atm. Filtn and evap. gave an oil, which was treated with excess CH_2N_2 in ether. The methylated material was chromatographed on prep. TLC (C_6H_6/ether, 9:1) to give XI (65 mg, R_f 0·5) and XII (60 mg, R_f 0·25).

XI M^+ 428: λ_{max} (C_6H_{12}) 220 and 232 nm (ε 16,700 and 7,200); ν_{max} (liquid film) 1755 (>CO, α,β-unsaturated γ-lactone), 1660 (>C=C<) and 1530, 1500, 1020, 875 and 755 (furan rings)[6,7] cm^{-1}; NMR ($CDCl_3$) 7·35 (1H, bs, furan α-H), 7·28 (1H, bs, furan α-H), 7·07 (1H, bs, furan α-H), 6·32 (1H, bs, furan β-H), 5·90 (1H, bs, furan β-H), 4·59 (1H, m, H-C-21), 4·07 (3H, s, OMe), 3·73 (2H, s, $C_4H_3OC\underline{H}_2C_4H_2O$—), 1·98 (3H, s, Me on C-23), 0·94 (3H, d, J = 6 Hz, sec-Me), 0·88 (3H, d, J = 6 Hz, sec-Me). (Found: C, 72·45; H, 8·35. $C_{26}H_{36}O_5$ requires C, 72·87; H, 8·47%).

XII, M^+ 428: λ_{max}(MeOH) 220 and 263 nm (ε 9,200 and 9,300); ν_{max} (liquid film) 1750 (w), 1700 (w), 1670 (w), 1610 (s) and 1150 (s) and 1550, 1500, 1145, 1020, 875 and 760 (furan rings)[6,7] cm^{-1}; NMR (CCl_4) 7·34 (1H, bs, furan α-H), 7·28 (1H, bs, furan α-H), 7·08 (1H, bs, furan α-H), 6·32 (1H, bs, furan β-H), 5·90 (1H, bs, furan β-H), 4·59 (1H, m, H-C-21), 4·00 (3H, s, OMe), 3·72 (2H, s, $C_4H_3O-\underline{CH}_2-C_4H_2O$—), 1·57 (3H, s, Me on C-23), 0·97 (3H, d, J = 6 Hz, sec-Me), 0·86 (3H, d, J = 6 Hz, sec-Me). (Found: C, 72·35; H, 8·41. $C_{26}H_{36}O_5$ requires: C, 72·87; H, 8·47%).

Ozonolysis of the mixture of ircinin-1 (I) and -2 (IV). The natural mixture of I and IV (200 mg) in EtOAc (50 ml) was ozonized (2% O_3) for 3 hr at −15°. After evap. of the solvent in *vacuo*, the ozonide was decomposed with water at 100° for 1 hr in the presence of a few drops of H_2O_2. The mixture was divided into two equal portions, portion a and b.

Portion a was extracted continuously for 5 hr with ether and the extract treated with excess CH_2N_2. After removal of solvents, the degradation products were analysed by GLC (5% SE-30 and 10% DEGS at 100° and 175°, respectively) and found to comprise methyl malonate, methyl succinate, methyl 2-oxohexanoate, methyl 2-methylglutarate and methyl 2-methyl-6-oxoheptanoate, by comparison with authentic samples. Authentic 2-methyl-6-oxoheptanoic acid was prepared by $KMnO_4$ oxidation of 1,3-dimethyl cyclohexene-1[8] according to Ruzika.[9]

Portion b was poured onto 200 ml of 2N HCl saturated with 2,4-dinitrophenylhydrazine and the dinitrophenylhydrazones formed were extracted with $CHCl_3$. After evapn of the solvent, the yellow residue in MeOH was treated with CH_2N_2 excess and the methylated mixture subjected to prep. TLC using C_6H_6/ether, 97:3, as eluent. The yellow band R_f 0·3 was scraped off and eluted with $CHCl_3$. After evapn of the solvent the residue was rechromatographed on prep. TLC using C_6H_{12}/EtOAc, 4:1, to give the dinitrophenylhydrazone of methyl 2-methyl-6-oxoeptanoate (R_f 0·6, 30 mg), M^+ 352, m.p. 70–71°, $[\alpha]_D$ = +10·2° (*c*, 1, $CHCl_3$), δ ($CDCl_3$) 3·69 (3H, s, OMe), 2·43 (3H, m, —$\underline{CH}_2$—C=N— and —$C\underline{H}$(Me)—CO_2Me), 2·03 (3H, s, Me —C=N—), 1·63 (4H, m, —N=C—CH_2—$\underline{CH_2CH_2}$—CH(Me)—), 1·19 (3H, d, J = 6 Hz, *sec*-Me) identical with a synthetic sample and the dinitrophenylhydrazone of methyl 2-oxohexanoate, identified by direct comparison (m.p., MS and NMR) with an authentic specimen.

Treatment with alkali of the mixture of ircinin-1 (I) and -2 (IV). To 200 mg of the natural mixture of I and IV a solution of KOH (8 g) in H_2O—EtOH (1:1, 12 ml) was added and the mixture refluxed for 2 hr. Evapn of EtOH, acidification with HCl and ether extn yielded a residue which was treated with excess CH_2N_2 in ether. The methylated mixture was purified by column chromatography (5 g SiO_2) in C_6H_6 and subsequent prep. TLC using C_6H_6/ether (95:5) to give 25 mg of a mixture of XV and XVI: λ_{max}(MeOH) 220 nm (ε 11,000); ν_{max} (liquid film) 3500 (OH), 1730 (CO, ester), 1220 (C—O—C, ester) and 3050, 1550, 1500, 1160, 1060, 1020, 875 and 760 (furan rings)[6,7] cm^{-1}; NMR (CCl_4) δ 7·35 (1H, bs, furan α-H), 7·28 (1H, bs, furan α-H), 7·07 (1H, bs, furan α-H), 6·32 (1H, bs, furan β-H), 5·90 (1H, bs, furan β-H), 3·72, 3·68 and 3·65 (each singlet integrating together for 8H, —OMe and $C_4H_3O-\underline{CH}_2-C_4H_2O$—), 2·69 (1H, m, —$C\underline{H}$(Me)—$CO_2$Me), δ 1·54 and 1·65 (each integrating together for 3H, Me—C=C), 1·14 (3H, d, J = 6 Hz, —CH(Me)—CO_2Me): MS, *m/e* (%) 474 (100, M^+), 415 (28, M^+—COOMe), 229 (18), 215 (56), 175 (35), 162 (85), 161 (20), 81 (45). (Found: C, 67·95, H, 8·02. $C_{27}H_{38}O_7$ requires: C, 68·33; H, 8·07%).

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