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STRUCTURES AND SYNTHESES OF HYPOLEPIN A, B AND C, SESQUITERPENES FROM HYPOLEPIS PUNCTATA METT.

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Three sesquiterpenoid constituents were isolated from leaves of Hypolepis punctata Mett. and their structures, I, II and III, were established by the synthesis.

Three sesquiterpenoid constituents, hypolepin A, B and C, have been isolated from leaves of a fern, Hypolepis punctata Mett. (Japanese name: Iwahimewarabi, Polypodiaceae family), and their structures have been established as I, II and III, respectively, based on the spectral and synthetic informations[1,2].

Hypolepin A, mp 87.5-88°, a chlorine containing compound[3], has a molecular formula $C_{15}H_{19}OCl$ [m/e 250.1136 (calcd. for M^+: 250.1124), 235.0900 (calcd. for $M^+ - CH_3$: 235.0889), 215.1442 (calcd. for $M^+ - Cl$: 215.1435); Analysis: Calcd.: C, 71.86; H, 7.63; Cl, 14.00%; Found: C, 71.80; H, 7.63; Cl, 14.25%]. Spectral data [$\nu_{max}^{CHCl_3}$ 1695, 1600 cm^{-1}; λ_{max}^{EtOH} 260, 295 nm (logε 4.21, 3.54); $\delta_{ppm}^{CDCl_3}$ 1.25 (6H, s), 2.49 (3H, s), 2.75 (3H, s), 2.93 (2H, s), 3.0-3.8 (4H, m), 7.18 (1H, br.s)] showed the presence of an aromatic conjugated carbonyl group and four tertiary methyl groups, two of which were assigned to be in arylic (2.49 and 2.75 ppm). A sharp six-proton singlet (1.25 ppm) and a two-proton singlet (2.93 ppm) appeared to be due to a gem-dimethyl and a benzylic methylene groups. The remaining four-proton multiplet at 3.0-3.8 ppm, other than one aromatic proton signal at 7.18 ppm, was roughly analyzed as A_2B_2 system arising from $Ar-CH_2-CH_2-Cl$ grouping. Reduction ($NaBH_4$ in ethanol) of hypolepin A gave a hydroxy compound (VII), mp 127-128°, $C_{15}H_{21}OCl$, $\nu_{max}^{CHCl_3}$ 3640 cm^{-1} (no carbonyl absorption); λ_{max}^{EtOH} 272.5, 276.5, 281 nm (logε 2.69, 2.59, 2.67); $\delta_{ppm}^{CDCl_3}$ 1.00 (3H,s), 1.22 (3H,s), 1.50 (OH), 2.34 (3H, s), 2.41 (3H, s), 2.60 (1H, s), 2.78 (1H, s), 2.90-3.80 (4H, m), 4.55 (1H, s), 6.86 (1H, br.s). Non-equivalency of the two geminal methyl groups and the two benzylic protons in VII, together with the facts that the carbinyl proton in VII was recognized as a sharp singlet at 4.55 ppm (5.91 ppm, singlet, in its acetate) and that the signal of one arylic methyl group (at C-7) displaced from 2.75 ppm in I to 2.41 ppm in VII, allowed us to propose the structure I for hypolepin A without confirmative evidences for the locations of the other arylic methyl (at C-5) and the chloroethyl (at C-6) groups.

Hypolepin B [II, mp 93-93.5°, $C_{15}H_{20}O_2$, $\nu_{max}^{CHCl_3}$ 3630, 1691, 1600 cm^{-1}; $\delta_{ppm}^{CDCl_3}$ 1.18 (6H, s), 1.70 (OH), 2.43 (3H, s), 2.70 (3H, s), 2.85 (2H,s), 3.17 (2H,

t, J=7), 3.77 (2H, t, J=7), 7.08 (1H, s)] gave a monoacetate (IV) [$\nu_{max}^{CHCl_3}$ 1728, 1690, 1600 cm^{-1}; $\delta_{ppm}^{CCl_4}$ 1.97 (s, $OCOC\underline{H}_3$), 4.00 (t, J=8, $C\underline{H}_2OAc$)] with acetic anhydride in pyridine, and a keto-aldehyde (V) [$\nu_{max}^{CHCl_3}$ 2700, 1720, 1690, 1600 cm^{-1}; $\delta_{ppm}^{CDCl_3}$ 3.70 (d, J=2, $ArC\underline{H}_2CHO$), 9.63 (t, J=2, $CH_2C\underline{H}O$)] by Collins' oxidation (CrO_3 in pyridine). Replacement of the hydroxyl group of II with chlorine ($POCl_3$ in pyridine) led II to hypolepin A (I).

Hypolepin C [III, mp 61-2°, $C_{16}H_{22}O_2$, $\nu_{max}^{CHCl_3}$ 1693, 1599 cm^{-1}; $\delta_{ppm}^{CDCl_3}$ 1.18 (6H, s), 2.37 (3H, s), 2.67 (3H, s), 2.83 (2H, s), 3.33 (3H, s), 2.9-3.6 (4H, m), 7.03 (1H, br.s)] was a methoxy-ketone. The structure was confirmed by derivation of II to III by methylation (CH_3I and t-BuOK).

Recently, two groups of workers[4,5] have reported the isolation of C_{14} and C_{15} indanone derivatives (or their glycosides) from Pteridium aquilium, a very close species to our plant. Hypolepin B was found to be identical with the compound HQ-2 by Natori et al[5] by direct comparison. Although the substitution pattern on the aromatic ring of hypolepins and other related natural indanones have been assigned mainly by the spectral bases, it is also supported by their possible biogenetic relationships with illudoids which have been discovered from fungal plants since 1962[6]; however, the final conclusion was obtained from the following synthesis of hypolepin B.

Friedel-Crafts' acetylation (CH_3COCl-$AlCl_3$ in CS_2) of ethyl β-(3,5-dimethylphenyl)propionate (VIII), prepared from ω-bromomesitylene by malonic ester condensation method, gave two isomeric acetyl derivatives, IXa [mp 46-7°, $\delta_{ppm}^{CCl_4}$ 2.18 (6H, s, $ArC\underline{H}_3$), 2.34 (3H, s, $COC\underline{H}_3$), 6.76 (2H, s, $Ar\underline{H}$)] and IXb [liquid, $\delta_{ppm}^{CCl_4}$ 2.16 (3H, s, $ArC\underline{H}_3$), 2.24 (3H, s, $ArC\underline{H}_3$), 2.37 (3H, s, $COC\underline{H}_3$), 6.72 (1H, s, $Ar\underline{H}$), 6.74 (1H, s, $Ar\underline{H}$)], in approximately 2:1 ratio. Transesterification of IXa with aluminum isopropoxide in 2-propanol, followed by reduction with diborane in tetrahydrofuran, gave a hydroxy-ester (X) in excellent yield[7], which was dehydrated ($SOCl_2$ in refluxing pyridine) and then hydrolyzed to give an olefinic acid (XI), $\nu_{max}^{CCl_4}$ 1700, 1630, 1610, 1565 cm^{-1}, $\delta_{ppm}^{CCl_4}$ 5.14 (1H,dd, J=18, 2), 5.41 (1H, dd, J=12, 2), 6.60 (1H, dd, J=18, 12) for the vinylic protons. Exposure of XI to an excess of trifluoroacetic anhydride at room temperature for 30 min. afforded an unsaturated indanone (XIII)[8], $\nu_{max}^{CHCl_3}$ 1690, 1630, 1595 cm^{-1}; $\delta_{ppm}^{CCl_4}$ 2.25 (3H, s), 2.50 (3H, s), 2.40-3.00 (4H), 5.12 (1H, dd, J=17, 2), 5.50 (1H, dd, J=12, 2), 6.68 (1H, dd, J= 17, 12), 6.96 (1H, s), as an almost homogeneous product after removal of the unchanged acid (XI). XIII was transformed by methylation (CH_3I and t-BuOK) to a 2,2-dimethylindanone derivative (VI), which was also formed from natural hypolepin A by elimination of hydrogen chloride (C_2H_5ONa in ethanol). VI was smoothly converted to a 2,4-dinitrophenylhydrazone (XIV), mp 213-216°, λ_{max}^{EtOH} 398 nm. Hydroboration (B_2H_6 in tetrahydrofuran, then OOH^-) of XIV, followed by the treatment with formic acid in the presence of copper carbonate[9] at 100°, gave hypolepin B, which was identical with the natural product in all respects.

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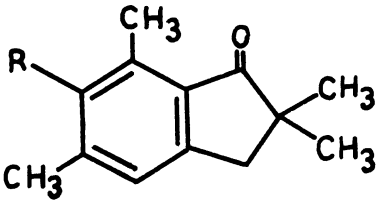


I R : $ClCH_2CH_2$-

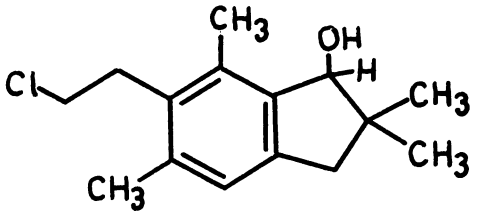
II R : $HOCH_2CH_2$-

III R : $CH_3OCH_2CH_2$-

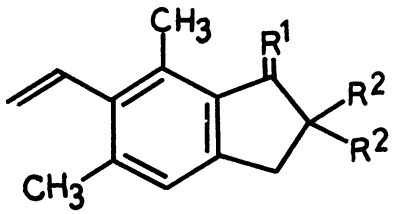
IV R : $AcOCH_2CH_2$-

V R : $OHCCH_2$-

VI R : CH_2=CH-

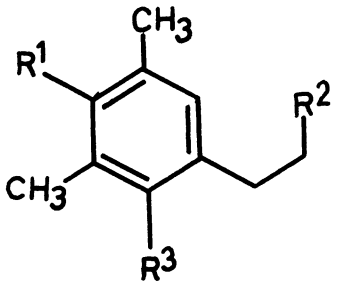


VII



XIII R^1 : =O, R^2 : H

XIV R^1 : 2,4-DNP, R^2 : CH_3



VIII R^1 : H, R^2 : $CO_2C_2H_5$, R^3 : H

IXa R^1 : CH_3CO-, R^2 : $CO_2C_2H_5$, R^3 : H

IXb R^1 : H, R^2 : $CO_2C_2H_5$, R^3 : CH_3CO-

X R^1 : $CH_3CH(OH)$-, R^2 : $CO_2C_3H_7^i$, R^3 : H

XI R^1 : CH_2=CH-, R^2 : CO_2H, R^3 : H

XII R^1 : $CH_3CH(OH)$-, R^2 : CH_2OH, R^3 : H

Footnotes and References

1. M. Nishizawa, Y. Hayashi and T. Sakan, Abstract for the 15th Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Osaka (1971) p. 141.
2. The name "pterosins", instead of "hypolepins", will be given for the compounds hereafter in order to avoid the confusion with the related natural indanones in the references[4,5]. According to this nomenclature[5b], hypolepins, A, B, and C, will be named pterosins, H, Z, and I, respectively.
3. Careful extraction from the original plant excluded any possibilities of introduction of the chlorine atom into I during the isolation process.
4. H. Hikino, T. Takahashi and T. Takemoto, Chem. Pharm. Bull. (Tokyo), 20, 210 (1972); H. Hikino, T. Takahashi, S. Arihara and T. Takemoto, ibid., 18, 1488 (1970).
5. K. Yoshihira, M. Fukuoka, M. Kuroyanagi and S. Natori, (a) Chem. Pharm. Bull. (Tokyo), 19, 1491 (1971); (b) ibid., 20, 426 (1972).
6. M. S. R. Nair, H. Takeshita, T. C. McMorris and M. Anchel, J. Org. Chem., 34, 240 (1969); N. Harada, K. Nakanishi, Chem. Commun., 310 (1970); other references are cited therein.
7. Diborane reduction of the ethyl ester (IXa) formed a dihydroxy compound (XII) as a sole product. Reactions with other reagents (e.g. $NaBH_4$ in ethanol or $Al(i\text{-}PrO)_3$ in toluene) gave similar undesirable results.
8. R. J. Ferrier and J. M. Tedder, J. Chem. Soc., 1435 (1957). Attempts to cyclize in other usual conditions (e.g. polyphosphoric acid) were not successful. Only product was 5,7-dimethylindanone which was also formed from VIII (R^2=COOH).
9. R. Robinson, Nature, 173, 541 (1954).

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