

FOUR NEW NEOLIGNANS FROM PIPER FUTOKADZURA

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(Received in Japan 20 September 1976; received in UK for publication 7 October 1976)

In the previous paper¹⁾, we reported the structure of piperenone, a neolignan having a hexahydrooxobenzofuran ring, isolated from the leaves of Piper futokadzura Sieb. et Zucc. From the same source, we have isolated four new neolignans, named isofutoquinol A and B and isodihydrofutoquinol A and B, together with futoquinol²⁾, which had already been isolated from the same plant. The present paper is concerned with the structures of these new neolignans.

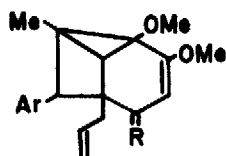
Isofutoquinol A (I) has mp 118-119°, C₂₁H₂₂O₅ (M⁺ 354.1443, calcd. 354.1467) and $[\alpha]_D \pm 0^\circ$. Its UV spectrum, λ_{\max} (EtOH) 233sh and 277 nm (ϵ 8390 and 9520), and IR spectrum, ν_{\max} (KBr) 1647, 1604, 1504 and 1492 cm⁻¹, suggest the presence of a substituted benzene and a conjugated ketone. The NMR spectrum (CDCl₃) of I showed the signals ascribed to a tertiary methyl (δ 1.59, 3H, s), two methoxyls (δ 3.38 and 3.53, each 3H, s), an allyl group (δ 2.53, 1H, dd, J=14, 8Hz; 2.89, 1H, dd, J=14, 6Hz; 5.1-5.3, 2H, overlap; 6.04, 1H, m) and a 3,4-methylenedioxyphenyl group (δ 5.84, 2H, s; 6.3-6.5, 2H, overlap; 6.62, 1H, d, J=8Hz). A broad singlet at δ 3.67 (1H) was ascribable to a benzylic proton by means of decoupling experiment; irradiation of this proton simplified the overlapped signals at δ 6.3-6.5 to a doublet (J=1.5Hz) and a double doublet (J=8, 1.5Hz). The remaining two singlets at δ 2.23 (1H) and 4.90 (1H) were assigned to a methine and an olefinic proton, respectively.

Reduction of I with LiAlH₄ in ether gave an alcohol (II), mp 115-117°; C₂₁H₂₄O₅ (M⁺ 356); λ_{\max} (EtOH) 238sh and 290 nm (ϵ 6000 and 4110); ν_{\max} (CHCl₃) 3561 cm⁻¹; δ (C₆D₆) 1.19 (1H, d, J=10.5Hz, exchangeable with D₂O, -CH-OH) and 4.39 (1H, brd, J=10.5Hz, collapsed to a broad singlet with D₂O, -CH-OH), which regenerated I on oxidation with active MnO₂ in benzene. The comparison of the UV, IR and NMR spectra between I and II indicates that I has an α,β -unsaturated carbonyl system in which the olefinic proton is located at the α -position for the NMR singlet at δ 4.90 for I was shifted to δ 4.18 and splitted with J=1.5Hz for II. When hydrogenated over 10%Pd-C in

MeOH, I gave a tetrahydro-derivative (III), mp 121-122°; $C_{21}H_{26}O_5$ (M^+ 358). The NMR spectrum ($CDCl_3$) of III showed the signals ascribed to a n-propyl group (δ 0.92, 3H, t, $J=7$ Hz; 1.1-1.8, 3H, overlap; 2.06, 1H, m). In addition, the methine proton (δ 1.57, d, $J=7.5$ Hz) was coupled to a new methine one (δ 2.59, m), which was exchangeable for a deuterium when III was treated with alumina in MeOD- D_2O under reflux. A two-proton singlet which newly appeared at δ 2.85 was assigned to benzylic methylene protons. The location of both the n-propyl group and the new methine proton at the α -position in the α,β -unsaturated carbonyl system in III was confirmed by means of reduction of III with $LiAlH_4$ in ether followed by treatment with silica gel in benzene affording a diene (IV), mp 50-52°; $C_{21}H_{26}O_4$ (M^+ -135, 207); λ_{max} (EtOH) 231sh and 284 nm (ϵ 7920 and 9270); ν_{max} no OH band. In the NMR spectrum ($CDCl_3$) of IV, the methine proton multiplet for III disappeared, and the signal of an olefinic proton newly appeared at δ 5.68 as a broad doublet ($J=7.5$ Hz), which was sharpened by irradiation of a methylene (δ 2.16, brt, $J=6.5$ Hz) in the n-propyl group; this olefinic proton was coupled to another olefinic one (δ 5.24, d, $J=7.5$ Hz). The methine proton doublet for III was collapsed to a singlet (δ 1.83) for IV. Accordingly, the partial structure of I can be represented by A.

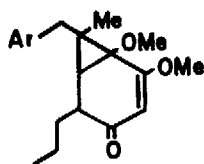
Treatment of II with HCl in MeOH gave an oily compound, $C_{21}H_{22}O_4$ (M^+ 338); λ_{max} (EtOH) 266 and 296sh nm (ϵ 13100 and 7340); ν_{max} no OH band; δ ($CDCl_3$) 2.11 (3H, d, $J=1.5$ Hz, $-CH=C-CH_3$), 3.76 and 3.82 (each 3H, s, $-OCH_3$), 6.24 (1H, q, $J=1.5$ Hz, $-CH=C-CH_3$) and 6.7-7.0 (5H, overlap, aromatic protons). This compound was identical with a trans-stilbene (V)² which was derived from futoquinol (VII) by reduction with $LiAlH_4$ in ether followed by treatment with HCl in MeOH. Therefore, a possible structure of isofutoquinol A should be represented by I.

Isofutoquinol B (VI) has the following physicochemical properties: mp 81-83°; $C_{21}H_{22}O_5$ (M^+ 354.1489, calcd. 354.1467); $[\alpha]_D \pm 0^\circ$; λ_{max} (EtOH) 237 and 288 nm (ϵ 12300 and 6270); ν_{max} (KBr) 1662, 1629, 1612, 1499 and 1487 cm^{-1} ; δ ($CDCl_3$) 1.95 (3H, d, $J=1$ Hz, $-CH=C-CH_3$), 2.94 and 3.54 (each 3H, s, $-OCH_3$), 2.98 (2H, brd, $J=6.5$ Hz, $-CH_2-CH=$), 4.9-5.3 (2H, overlap, $-CH=CH_2$), 5.34 (1H, s, $-CO-CH=$), 5.83 (1H, qt, $J=17.5, 9, 6.5$ Hz, $-CH_2-CH=CH_2$), 5.86 (2H, s, $-OCH_2O-$), 6.15 (1H, t, $J=1.5$ Hz, $-CH=C-CH_2-$), 6.3-6.5 (3H, overlap, $-CH=C-CH_3$ and aromatic protons) and 6.60 (1H, d, $J=8$ Hz, aromatic proton); m/e 354 (M^+), 313 (base peak), 285, 282, 194, 179, 135 and 103. The mass spectrum is almost identical with that of futoquinol (VII)², and also the IR and NMR spectra indicate the presence of the same functional groups as VII. However, VI is different from VII, which has the E-configuration for the styryl moiety, with respect to UV absorptions and chemical shifts of NMR signals. VI absorbed at shorter wavelengths than VII (260 and 295 nm, ϵ 16700 and

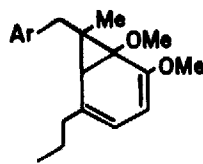


(I) R = O

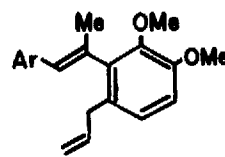
(II) R = H, OH



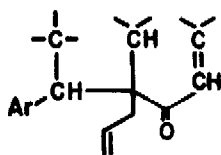
(III)



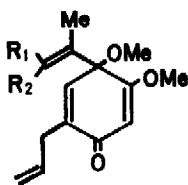
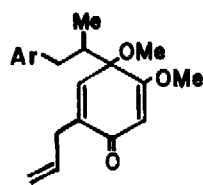
(IV)



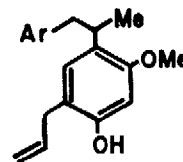
(V)



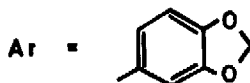
(A)

(VI) R₁ = H, R₂ = Ar(VII) R₁ = Ar, R₂ = H

(VIII)



(IX)



10760), and the signal of the vinyl methyl for VI appeared at lower field than that for VII (δ 1.68). On the basis of the above data, isofutoquinol B is concluded to be Z-isomer of VII (VI).

Isodihydrofutoquinol A (VIIIa) and B (VIIIb) are colorless oils and the same molecular formula, C₂₁H₂₄O₅ (M⁺ 356.1628 and 356.1621, respectively, calcd. 356.1623). Their mass spectra are identical (m/e 356 M⁺, 194, 163 base peak, 135 and 105), but their specific rotations are different ($[\alpha]_D$ -19.6°, c=1.31, MeOH, and +92.0°, c=1.25, MeOH, respectively). The other spectral properties of both VIIIa and VIIIb are quite similar to each other, and also to those of isofutoquinol B (VI), except that the NMR signals of CH₃-CH-CH₂- units (δ 0.93, 3H, d, J=7Hz; 1.96, 1H, dd, J=13, 9Hz; ca. 2.4, 1H, m; 2.60, 1H, dd, J=13, 3Hz, for VIIIa and δ 0.58, 3H, d, J=7Hz; 1.8-2.5, 3H, overlap, for VIIIb) appeared in place of those of the CH₃-C=CH- unit for VI: VIIIa, λ_{\max} (EtOH) 236 and 287 nm (ϵ 15600 and 8070); ν_{\max} (CHCl₃) 1664, 1632, 1610, 1506 and 1492 cm⁻¹; δ (CDCl₃) 3.09 and 3.74 (each 3H, s), 3.13 (2H, brd, J=6.5Hz), 4.9-5.3 (2H, overlap), 5.71 (1H, s), 5.87 (2H, s), 5.93 (1H, qt, J=17.5, 9, 6.5Hz), 6.31 (1H, t, J=1.5Hz), 6.4-6.6 (2H, overlap) and 6.66 (1H, d, J=8Hz), and VIIIb, λ_{\max} (EtOH) 236 and 287 nm (ϵ 16800 and 8660); ν_{\max}

(CHCl₃) 1665, 1631, 1610, 1504 and 1490 cm⁻¹; δ (CDCl₃) 3.13 and 3.74 (each 3H, s), 3.13 (2H, brd, J=6.5Hz), 4.9-5.3 (2H, overlap), 5.71 (1H, s), 5.87 (2H, s), 5.93 (1H, qt, J=17.5, 9, 6.5Hz), 6.30 (1H, t, J=1.5Hz) and 6.66 (3H, s). The above data indicate that VIIIa and VIIIb are diastereomers and each of them consists of the CH₃-CH-CH₂- unit, a 3,4-methylenedioxyphenyl group and an 2-allyl-4,5-dimethoxy-2,5-cyclohexadienone moiety. The combination of the CH₃-CH-CH₂- unit and the methylenedioxyphenyl group to form an α -methylphenethyl moiety in each of VIIIa and VIIIb was determined on the basis of its mass spectrum (m/e 163, C₁₀H₁₁O₂, and 135, C₈H₇O₂), and the presence of the cyclohexadienone moiety was verified by means of zinc reduction of the mixture of VIIIa and VIIIb (ca. 1 : 4) in acetic acid affording a phenol (IX), mp 63-66°; C₂₀H₂₂O₄ (M⁺ 326); $[\alpha]_D$ -61.6° (c=0.70, MeOH); λ_{max} (EtOH) 225sh and 286 nm (ϵ 13500 and 8580); ν_{max} (CHCl₃) 3593 and 3518 cm⁻¹; δ (CDCl₃) 3.70 (3H, s, -OCH₃), ca. 5.1 (1H, overlap, exchangeable with D₂O, OH), 6.35 and 6.82 (each 1H, s, aromatic proton) and 6.4-6.8 (3H, overlap, aromatic protons). Thus, the structures of both isodihydrofutoquinol A and B should be represented by VIII.

Finally, isofutoquinol A (I) and B (VI) were derived from futoquinol (VII) by irradiation with sunlight in *n*-hexane, and also isofutoquinol B was converted to futoquinol and isofutoquinol A in the same manner. Such conversions raise the question of whether or not isofutoquinol A and B actually occurred in nature. It is interesting to note that the rare neolignan having a bicyclo [2.2.0]hexane ring, isoasatone³⁾, which was derived from asatone by photochemical cycloaddition⁴⁾, has recently been isolated.

Acknowledgement: The authors wish to express their deep gratitude to Prof. Y. Hatsuda and Dr. T. Hamasaki, Tottori University, for their encouragement, to Dr. H. Mishima, Sankyo Co. Ltd., for the generous gift of futoquinol, and to Drs. S. Hosozawa and S. Kogiso, Nagoya University, for the measurements of NMR and mass spectra and optical rotations.

References

- 1) K.Matsui and K.Munakata, Agri. Biol. Chem., **40**, 1113 (1976).
- 2) S.Takahashi and A.Ogiso, Chem. Pharm. Bull., **18**, 100 (1970).
- 3) K.Sasaki, Y.Hirata, S.Yamamura, Y.Chen, M.Hong and H.Hsu, Tetrahedron Letters, **1973**, 4881.
- 4) S.Yamamura, Y.Terada, Y.Chen, H.Hsu and Y.Hirata, ibid., **1975**, 1903.