CHEMISTRY LETTERS, pp. 301-304, 1978. Published by the Chemical Society of Japan

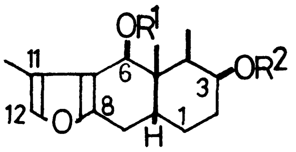
THE REVISED STRUCTURE OF FURANOFUKINOL, A CONSTITUENT FROM PETASITES JAPONICUS MAXIM. RHIZOMES

Keizo NAYA, Yasuo MAKIYAMA, Takashi MATSUURA, Nobuo II,
Hajime NAGANO,* and Takeyoshi TAKAHASHI*
Department of Chemistry, Faculty of Science, Kwansei Gakuin
University, Uegahara, Nishinomiya, Hyogo 662
* Department of Chemistry, Faculty of Science, The University of Tokyo,
Bunkyo-ku, Tokyo 113

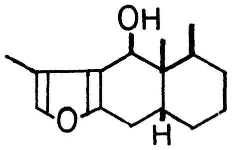
The structure of furanofukinol, a constituent of Petasites japonicus Maxim., proposed previously as 3α,6β-dihydroxyfuranoeremophilane (V-a) should be revised to 3β,6β-dihydroxyfuranoeremophilane (I) by the PMR study of 3-O-angeloyl-6-O-acetylfuranofukinol (VIII) and by the chemical conversion of furanofukinol to 3β-hydroxyeremophilanes (X-a,b). The structures of the two related sesquiterpenes, isolated from Farfugium hiberniflorum Kitam., must therefore be revised to 3β-angeloyloxy-6β-hydroxyfuranoeremophilane (VII) and 3β-angeloyloxy-6β-acetoxyfuranoeremophilane (VIII).

Furanofukinol (I) and its esters have been isolated as the main components from Petasites japonicus Maxim. rhizomes. In a preliminary communication,1) the stereochemistry of furanofukinol except for the configuration of the 3-OH was established by conversion to the known petasalbin (II),2) ligularone (III),3) and 6-oxofuranoeremophil-3-ene (IV). The remaining configurational assignment was therefore drawn tentatively to be 3α(eq)-OH as in the formula (V-a) from the analogous PMR signals due to 3(ax)-H ($W^1/_2$=ca. 14 Hz) observed for furanofukinol and the known isopetasol [VI; with 3α(eq)-OH],4) on the assumption that furanofukinol adopts a steroidal conformation. Shortly after the two new compounds, $C_{20}H_{28}O_4$ and $C_{22}H_{30}O_5$, isolated from Farfugium hiberniflorum Kitam. were suggested to be 3-O-angeloylfuranofukinol (V-b; now revised to VII) and 3-O-angeloyl-6-O-acetylfuranofukinol (V-c; now revised to VIII), respectively, by their conversion to furanofukinol.5) In the detailed PMR study of VIII6) the 3-H signal was observed as a quintet due to a large diaxial ($J_{2\beta,3\alpha}$=12 Hz) and two smaller axial-equatorial ($J_{2\alpha,3\alpha}=J_{3\alpha,4\alpha}$=6 Hz) vicinal couplings. This can only be explained based on the structure (VIII) with 3β(eq)-OH group in a non-steroidal conformation7) as in the formula (I-A). This would require revision for the structure of furanofukinol from V-a to I. In order to obtain chemical evidence showing the 3β-OH configuration for furanofukinol (I), both I and the known tetrahydroisopetasol (IX)8) have now been converted to 3-hydroxyeremophilanes (X-a,b,c)9) and then to the corresponding 3-oxo derivatives (XI-a,b). 3-Hydroxyeremophilanes derived from I were found to be 3β-hydroxy-7βH- (X-a) and 3β-hydroxy-7αH-eremophilane (X-b) as will be described below.

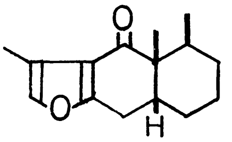
The photooxygenation procedure10) similar to that described previously for



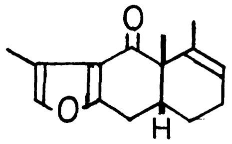
R1 R2
I : H H
VII : H } $\mathrm{OC{-}C(Me){=}C(Me)H}$
VIII : Ac }



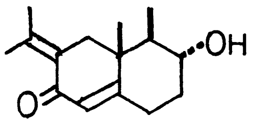
II



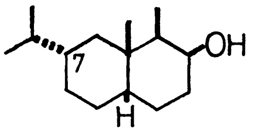
III



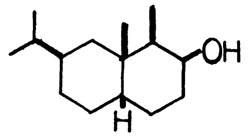
IV



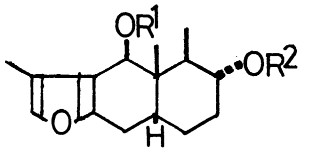
VI



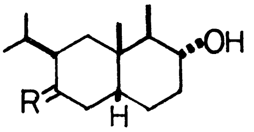
X-a



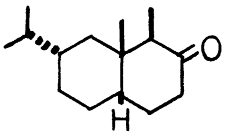
X-b



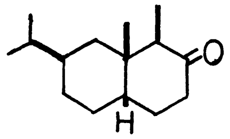
R1 R2
V-a : H H
V-b : H } $\mathrm{OC{-}C(Me){=}C(Me)H}$
V-c : Ac }



R
IX : O
X-c : H_2



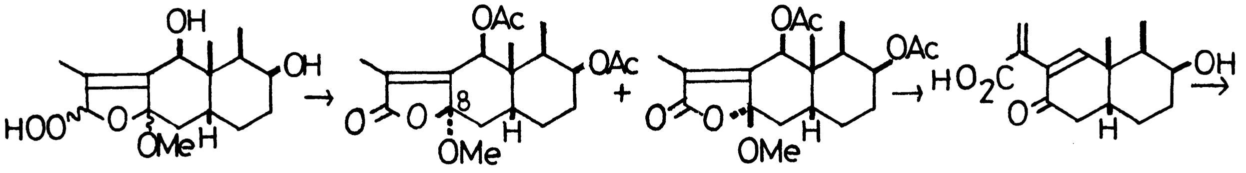
XI-a



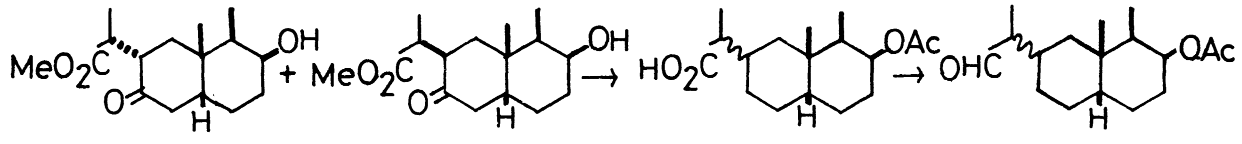
XI-b

petasalbin (II) was applied for cleavage of the furan ring of I. The oxygenation of I gave a mixture of hydroperoxides [XII; positive to a peroxide-test (KI-AcOH)] showing two spots on TLC. The mixture (XII) was treated with Ac_2O-pyridine to afford quantitatively a diastereomeric mixture (XIII-a,b), which was chromatographed on silica gel. Elution with light petroleum-ether (10:1) and subsequent recrystallization from diisopropyl ether gave an 8α-methoxy lactone (XIII-a), mp 132.5-133°, $[\alpha]_D$ -198° (c, 1.05, $CHCl_3$) and an 8β-methoxy lactone (XIII-b), mp 139-140°, $[\alpha]_D$ +180° (c, 1.00, $CHCl_3$). These assignments were given on the basis of the generalization$^{10)}$ outlined previously. The mixture (XIII-a,b) was treated with an excess of alkali to afford quantitatively an acid as the sole product (XIV), $C_{15}H_{20}O_4$, mp 163.5-164°. Its spectral data were compatible with the structure XIV; IR(KBr): 3360 (OH), 1703 (COOH), 1670 (unsaturated ketone), 1618, 945 cm^{-1} (terminal methylene); UV(MeOH): λ_{max} 218 (ε, 8250), 243 nm (ε, 9140); δ(acetone-d_6): 6.98 (m, COOH and OH), 6.69 (d, J=1.5 Hz, 6-H), 6.11 and 5.68 (each d, J=1.5 Hz, 13-CH_2), 3.76 (sex, J=5.5, 6, and 6 Hz, $W^1/_2$=12 Hz, 3-H), 1.28 (s, 15-Me), 0.98 (d, J= 7.4 Hz, 14-Me). The acid (XIV) was subjected to hydrogenation in KOH-aq MeOH in the presence of 5% Pd-C, epimerization in KOH-MeOH under reflux in a N_2 atmosphere, and then to esterification with CH_2N_2 in ether to give a mixture of esters. The mixture was separated by chromatography on silica gel [eluted with benzene-AcOEt (20:1)] into two esters, (XV-a), an oil, $[\alpha]_D$ -44° (c, 1.21, $CHCl_3$) and (XV-b), mp 71.2-72.2°, $[\alpha]_D$ +65.6° (c, 1.04, $CHCl_3$). A distinct difference between the two esters was observed on the signals due to 3-H in their PMR spectra; δ($CDCl_3$): 4.01

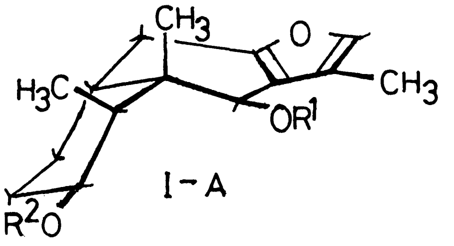
(br m, $W^1/_2$=19 Hz) for XV-a and $\delta(CCl_4)$: 3.87 (m, $W^1/_2$=7.2 Hz) for XV-b. This suggested that XV-a adopts a non-steroidal conformation, while XV-b a steroidal conformation in the solution (vide infra). The presence of diastereomers due to C-11 asymmetric center could not be detected for these esters (XV-a,b) as well as for the products (XVI and XVII).[11] The mixture (XV-a,b) was subjected successively to acetylation, thioketalization, desulfurization, alkaline hydrolysis, and to reacetylation to give an acetoxy acid (XVI) as an oil. The acid (XVI) was treated with N,N'-carbonyldiimidazole and then reduced with $LiAl(t\text{-}BuO)_3H$ to yield an oily aldehyde [XVII; IR(film): 2670, 1723 cm^{-1} (CHO)], via imidazolide.[12] Thioketalization of XVII and subsequent desulfurization gave 3-acetoxyeremophilane (XVIII) as an oil. Hydrolysis of XVIII yielded an oily product, which was shown to consist of the two isomers (X-a and X-b, in a ratio of 3.3:1) by GLC examination (SPE, 2 m; column temp, 160°; N_2-flow rate, 40 ml/min; retention time: X-a, 41.6 min; X-b, 27.9 min). The isomeric mixture was separated by chromatogrphy on silica gel [eluted with light petroleum-ether (50:1)], and was purified by PGLC (SF 96, 1.85 m; column temp, 160°; retention time: X-a, 23.7 min; X-b, 18.4 min).



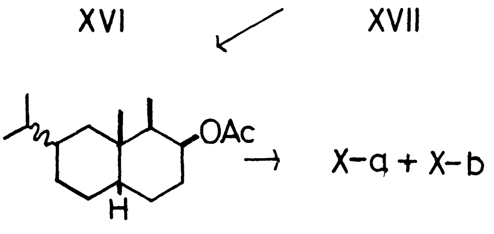
XII XIII-a XIII-b XIV



XV-a XV-b XVI XVII



I-A



XVIII

The isomeric 3-hydroxyeremophilanes, $C_{15}H_{28}O$ (by elemental analysis), showed the following spectra, respectively; X-a: an oil, $[\alpha]_D$ -74.2° (c, 0.96, $CHCl_3$); IR (film): 3315, 1051 cm^{-1} (OH); $\delta(CCl_4)$: 3.95 (ddd, J=5, 6.5, and 12 Hz, $W^1/_2$=18 Hz, 3α(ax)-H); X-b: an oil, $[\alpha]_D$ +34.5° (c, 1.46, $CHCl_3$); IR(film): 3375, 1023 cm^{-1} (OH); $\delta(CCl_4)$: 3.74 (sex, J=5.5, 5, and 5 Hz, $W^1/_2$=7.5 Hz, 3α(eq)-H.[9] On the other hand, 3α(eq)-hydroxy-7αH- eremophilane (X-c),[9] mp 90-91°, $[\alpha]_D$ +5.0° (c, 1.07, $CHCl_3$), derived from tetrahydroisopetasol (IX)[8] with the known configuration proved to be different from the isomers (X-a,b) in comparison of their GLC, IR, and PMR data; X-c: 33.9 min (the same conditions as above, SPE); IR($CHCl_3$): 3580, 1010 cm^{-1} (OH); δ($CDCl_3$): 3.52 (sex, J=5, 10, and 10 Hz, $W^1/_2$=18 Hz, 3β(ax)-H). Therefore, a pair of isomers at C-7 (X-a and X-b) were readily assumed to adopt a non-steroidal and a steroidal conformation, respectively, on the basis of the J-values of the 3-H, and consequently these isomers should be 3β(eq)-hydroxy-7βH- and 3β (ax)-hydroxy-7αH-eremophilane, respectively. As would be expected from the above conclusion, the same oily 3-oxo derivative (XI-b),13) $[\alpha]_D$ -4.1° (c, 0.97, $CHCl_3$), was obtained from X-b and X-c. However, this ketone (XI-b) was found to be different from oily 3-oxoeremophilane (XI-a),13) $[\alpha]_D$ -69.5° (c, 0.87, $CHCl_3$) derived from X-a in comparison of their GLC, IR, and PMR data.

The structure of furanofukinol should now be revised from V-a to I, and its PMR spectrum1) can well be explained based on the non-steroidal conformation (I-A; R=H), 3β(eq),6β(pseudoeq)-dihydroxyfuranoeremophilane. The 3β-OR^2 configuration for the related compounds (VII and VIII) was also shown.

References

1) K. Naya, M. Nakagawa, M. Hayashi, K. Tsuji, and M. Naito, Tetrahedron Lett., 1971, 2961.

2) L. Novotný, V. Herout, and F. Šorm, Collect. Czech. Chem. Commun., 29, 2189 (1964); H. Ishii, T. Tozyo, and H. Minato, J. Chem. Soc., (C), 1966, 1545.

3) H. Ishii, T. Tozyo, and H. Minato, Tetrahedron, 21, 2605 (1965).

4) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, Y. Hirose, and N. Shinoda, Tetrahedron, 24, 5871 (1968).

5) H. Nagano and T. Takahashi, Bull. Chem. Soc. Jpn., 45, 1935 (1972).

6) H. Nagano, Ph. D. Thesis, The University of Tokyo, Tokyo Japan, 1973.

7) Several furanoeremophilanes have been reported to adopt non-steroidal conformations: H. Nagano, Y. Tanahashi, Y. Moriyama, and T. Takahashi, Bull. Chem. Soc. Jpn., 46, 2840 (1973).

8) I. Takagi, Y. Tazuke, and K. Naya, Bull. Chem. Soc. Jpn., 50, 3320 (1977).

9) The other properties of X-b and X-c will be reported in a full paper.

10) K. Naya, R. Kanazawa, and M. Sawada, Bull. Chem. Soc. Jpn., 48, 3220 (1975); K. Naya, N. Nogi, Y. Makiyama, H. Takashina, and T. Imagawa, ibid., 50, 3002 (1977); detailed description on XIII-a and XIII-b will be presented in a full paper.

11) The saturated lactone transformed from XV-a by reduction with $NaBH_4$ has been found to consist of the C-11 diastereomers: details will be reported soon.

12) H. A. Staab and H. Bräuling, Justus Liebigs Ann. Chem., 654, 119 (1962).

13) Detailed data on XI-a and XI-b will be reported in a full paper.

(Received January 18, 1978)