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THE SESQUITERPENES OF CACALIA SPECIES: 8-OXOCACALOL AND THE STEREOCHEMISTRY OF CACALONE EPIMERS

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A new sesquiterpene has been isolated from Cacalia delphiniifolia Sieb. et Zucc. and its structure has been assigned to 8-oxocacalol (I) by physical and chemical methods. Cacalone (VIb) and the C-4 epimer (VIa) have been first obtained from the natural source (the above plant), and also by photosensitized oxygenation or autoxidation of cacalol (II). The stereochemistry of the epimers was established by comparisons of physical and chemical properties between the isomers and their acetates (VIIb and VIIa).

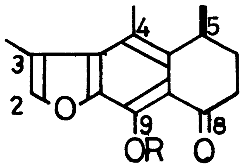
In connection with our investigation,[1,2] we have further isolated a new sesquiterpene (I) as a minor component from the benzene extract of the roots of Cacalia delphiniifolia Sieb. et Zucc. (Japanese name 'Momijigasa'). The isolation was performed by repeated column chromatography with silica gel [Rf 0.55, as compared with Rf 0.53 of cacalol (II) on TLC (SiO_2, benzene)]. The compound I proved to be 8-oxocacalol, which was once proposed for the structure of cacalone,[3] as follows.

Compound I, yellow plates, mp 108-109°C (from diisopropyl ether), $C_{15}H_{16}O_3$ (MS: m/e 244, M^+ and base peak, and elemental analysis), $[\alpha]_D^{23}$ -15° (c, 1.07, $CHCl_3$), was positive to $FeCl_3$ test (green), and its IR ($CHCl_3$) spectrum exhibits bands attributable to a (H-bonded) phenolic OH, a conjugated C=O, and a furan ring; 3400-2600 (broad), 1650, and 1560 and 880 cm^{-1}. PMR ($CDCl_3$): A pair of signals at δ 2.35, d, J=1 Hz and 7.41, q, J=1 Hz, characteristic of the β-methylfuran grouping, and a signal due to a strongly chelated phenolic proton at 13.5, br s, 1H (exchangeable with D_2O). Other signals were at δ 1.24 (d, J=7 Hz, 5-Me), ca. 2.0 (m, 2H), 2.48 (s, 4-Me), ca. 2.75 (m, 2H), and ca. 3.35 (m, 1H). The PMR spectrum similar to that of cacalol (II) and the chelation suggest the presence of a carbonyl group at the peri-position (C-8) to the phenolic OH group.

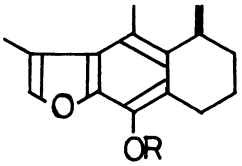
Treatment of I with MeI - K_2CO_3 in acetone gave quantitatively a methyl ether (III), mp 72-74°C (colorless prisms from diisopropyl ether), $C_{16}H_{18}O_3$ (MS: m/e 258, M^+ and base peak, and elemental analysis), $[\alpha]_D^{25}$ -45° (c, 1.06, $CHCl_3$). IR absorption and PMR signal due to a chelated OH group are not observed on the methyl ether III; IR ($CHCl_3$): 1670 cm^{-1} (a conjugated C=O); PMR ($CDCl_3$): δ 7.40 (q, J=1 Hz, 2-CH), 4.10 (s, MeO), ca. 3.4 (m, 5-CH), ca. 2.75 (m, 7-CH_2), 2.57 (s, 4-Me), ca. 2.50 (m, 6-CH_2), 2.39 (d, J=1 Hz, 3-Me), and 1.25 (d, J=7 Hz, 5-Me).

Two D atoms were incorporated (m/e 260, M^+) when III was treated with a catalytic amount of MeONa in MeOD at 60°C in a sealed tube. Finally III was transformed into cacalol methyl ether (IV) via ethylene thioketal (V) and subsequent reduction with Raney nickel in EtOH. Compound IV was identical in all respects with the authentic cacalol methyl ether.

The reported spectral data of synthetic (±) 8-oxocacalol, mp 115°C,[4] are in close agreement with those of I.



I R = H
III R = Me



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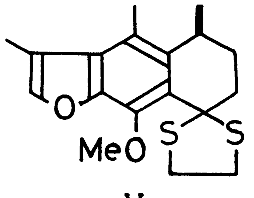
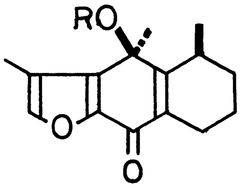
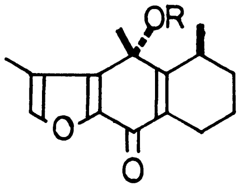


V



VIa R = H
VIIa R = Ac



VIb R = H
VIIb R = Ac

Previously we reported the isolation of cacalone[2] from the same plant, and also its synthesis from cacalol (II) by autoxidation[2] and photosensitized oxygenation.[1] Our continued investigation revealed that the natural and synthetic 'cacalone' consists of the C-4 epimeric mixture (VIa and VIb).

Column chromatography of the natural 'cacalone' part (ca. 1:1 mixture of

VIa and VIb as indicated by its PMR spectrum) with Al_2O_3 (grade II; light petroleum - ether, 15:1) gave epicacalone (VIa), mp 129.5-131°C (colorless needles from diisopropyl ether - acetone), $[\alpha]_D^{25}$ +95° (c, 0.980, $CHCl_3$). Further elution afforded cacalone (VIb), mp 139-141°C (colorless prisms from diisopropyl ether - acetone), $[\alpha]_D^{25}$ +87° (c, 1.00, $CHCl_3$). VIa and VIb showed similar physical (adsorption) and spectral (UV, IR and PMR) properties (Table 1).5)

Acetylation of cacalone (VIb) with Ac_2O - pyridine at room temperature gave cacalone acetate (VIIb) in a nearly quantitative yield; mp 166-167°C (colorless prisms from MeOH - acetone), $[\alpha]_D^{25}$ +25° (c, 1.07, $CHCl_3$). In contrast, acetylation of epicacalone (VIa) hardly proceeded under similar conditions, but at 70°C yielded epicacalone acetate (VIIa) in a high yield; mp 145-146.5°C (colorless prisms from diisopropyl ether), $[\alpha]_D^{25}$ +56° (c, 1.07, $CHCl_3$). The acetates, VIIa and VIIb, were confirmed to be C-4 epimers to each other by comparison of MS (m/e 288, M^+), microanalysis and their spectral data (IR, PMR and UV). These acetates have the same Rf value, 0.47 (SiO_2; benzene - ethyl acetate, 10:1), and show small differences in the finger print region (IR) and the chemical shifts of C-4 and C-5 methyl protons (PMR) (Table 1). Cacalone acetate (VIIb) was also prepared in ca. 35% yield by treatment of cacalol (II) with a slight excess of lead tetraacetate in benzene at room temperature according to the Yuste's method.6)

Cacalone acetate (VIIb) was easily hydrolyzed in a refluxing aqueous MeOH solution with $KHCO_3$ to afford cacalone (VIb) quantitatively. However, epicacalone acetate (VIIa) resisted the hydrolysis, and gave the parent alcohol (VIa) only in a poor yield after prolonged reaction.

The observed differences in the reactivities between the pairs of epimers upon acetylation and hydrolysis are interpreted in terms of the different stereochemical circumstances at C-4 as shown in the formulas, VIa,b and VIIa,b. Their PMR data also support the above configurational assignments. Thus the 5β-methyl signal (δ 1.31) of the less reactive epicacalone (VIa) resonates at lower field than that (δ 1.24) of cacalone (VIb) (proximity effect7) of the 4β-OH group), while acetylation of VIa induced an upfield shift ($\Delta\delta$ = 0.21 ppm) (anisotropic effect8) of the 4β-OAc group).

Table 1. Spectral Properties of Cacalone Epimers and Their Acetates.

Compound	PMR ($CDCl_3$), δ						IR ($CHCl_3$), cm^{-1}
	2-H	3-Me	4-Me	4-OH	4-$OCOCH_3$	5-Me	
VIa*	7.30q J=1Hz	2.22d J=1Hz	1.60s	2.55s		1.31d J=7Hz	3580, 3400br, 1660
VIb*	7.29q J=1Hz	2.22d J=1Hz	1.63s	2.80s		1.24d J=7Hz	3560, 3400br, 1660
VIIa**	7.36q J=1Hz	2.08d J=1Hz	1.66s		2.07s	1.10d J=7Hz	1743, 1660
VIIb**	7.34q J=1Hz	2.09d J=1Hz	1.70s		2.11s	1.30d J=7Hz	1740, 1660

* $C_{15}H_{18}O_3$, from MS (m/e 246, M^+) and microanalysis.

** $C_{17}H_{20}O_4$, from MS (m/e 288, M^+) and microanalysis.

REFERENCES AND NOTES

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3) H. Kakisawa and Y. Inouye, Tetrahedron Lett., 1969, 1929.
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5) From *Cacalia decomposita*, Romo and his coworkers isolated compounds with mp 119-120°C and mp 140-143°C, which originally were assumed to be the same substance after all. It is only recently that structure VIa for the former and VIb for the latter have been given after a series of revisions. This paper deals with an unambiguous description of both the isolation and the structural assignment of cacalone epimers. Confer ref. 6 and references cited therein.
6) F. Yuste, E. Díaz, and F. Walls, J. Org. Chem., 41, 4103 (1976). According to them, hydrolysis of VIIb thus prepared, with $KHCO_3$ - H_2O in MeOH gives a 1:1 mixture of VIa and VIb. We, however, obtained VIb as the sole product.
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