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OXYGENATED CYCLOHEXANES FROM *PIPER CUBEB*

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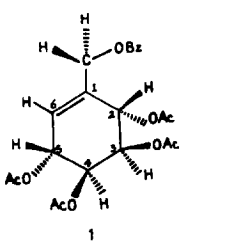
Abstract—Further investigation of the petrol extract of *Piper cubeb* yielded two new minor oxygenated cyclohexanes, (−)-rel-(2*S*,3*R*,4*R*,5*R*)-2,3,4,5-tetraacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol[(−)-piperenol C] and (+)-(2*S*,3*R*,4*R*,5*R*)-2,4,5-triacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate[(+)-piperenol A-triacetate]. In addition, two rare neolignans have been isolated for first time from this species and identified as (−)-kadsurin A and (−)-piperenone.

INTRODUCTION

In continuation of our work on the phytochemical analysis of Indian *Piper* [1] and our work related to the isolation and structural elucidation of three new oxygenated cyclohexanes, namely, (+)-piperenol A and (+)-piperenol B from the petrol extract of *P. cubeb* and acetyl piperenol A from the petrol extract of *P. clarkii* [2], we now report the results of further exhaustive chemical investigations of the petrol extract of *P. cubeb* and the isolation and structural elucidation of minor constituents of which two are the new oxygenated cyclohexanes, **1** and **2**, and two are the neolignans kadsurin A (**3**) and piperenone (**4**), not previously reported from this species.



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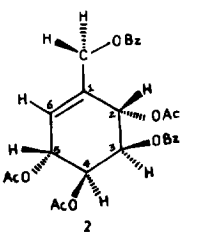

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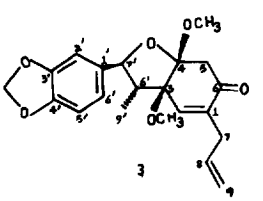

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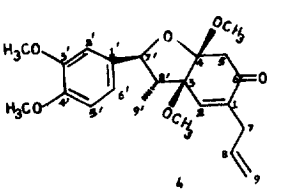

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RESULTS AND DISCUSSION

Compound **1**, which could not be crystallized, analysed for $C_{22}H_{24}O_{10}$ ([M]$^+$ *m/z* 448). The ^{1}H NMR of **1** had all the characteristics of an oxygenated cyclohexane. The signals for the aromatic protons of a benzoyl moiety were located at δ7.42–7.52 and δ8.0–8.10, respectively. Four sharp singlets, each integrating for three protons, were present at δ1.98, 2.02, 2.08 and 2.12, and were assigned to four acetoxyl methyl group protons. A double doublet at δ 4.76 (J = 0.8 Hz and 12.5 Hz) integrating for one proton and a corresponding double doublet at δ5.06 (J = 0.5 Hz and 12.5 Hz) were attributed to an allylic methylenoxy group. A double doublet at δ6.13 integrating for one proton (J = 3.7 Hz and 0.47 Hz) was assigned to the olefinic proton (H-6). The doublet for H-2 was located at δ5.68 (J = 7.4 Hz). Three other double doublets positioned at δ5.80 (J = 2.7 Hz and 0.3 Hz), δ5.90(J = 0.3 Hz and 2.7 Hz) and δ5.94 (J = 2.7 Hz and 3.7 Hz) were assigned, respectively, to H-3, H-4 and H-5 correlated through their coupling constants. The stereochemical assignments and correlations among H-2, H-3, H-4 and H-5 were further established by double-irradiation experiments. Thus, irradiating the doublet at δ5.68 (H-2) resulted in the appearance of a weak doublet at δ5.80 (J = 0.3 Hz) for H-3. When H-3 at δ5.80 (*dd*) was irradiated, it resulted in the appearance of a singlet at δ5.68 for H-2 and a doublet at δ5.90 (J = 2.7 Hz) for H-4. Similarly, irradiation of the signal for H-4 at δ5.90 changed those for H-3 and H-5 from double doublets to doublets. On the basis of the above data, compound **1** is assigned the structure (−)-rel-

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(2*S*,3*R*,4*R*,5*R*)-2,3,4,5-tetraacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol and it is designated (−)-piperenol C. This is the first report of the occurrence of a laevorotatory oxygenated cyclohexane derivative from *P. cubeb*; other similar oxygenated cyclohexanes isolated from this species are dextrorotatory [2].

Compound **2** was crystalline solid. It analysed for $C_{27}H_{26}O_{10}$ ($[M]^+$ *m/z* 510). The ^1H NMR of **2** was also typical of a substituted cyclohexane system wherein signals for 10 benzoyl protons appeared at δ7.45–7.57 and δ7.94–8.01, respectively. Three singlets for acetoxylmethyls were observed at δ2.07, 2.11 and 2.16, respectively. A double doublet at δ4.84 (J = 14.3 Hz and 1.5 Hz) for one proton and a corresponding double doublet at δ4.88 (J = 14.3 Hz and 0.8 Hz) were assigned to the methylenoxy protons. An olefinic proton signal (H-6) was located downfield at δ6.12 as a double doublet (J = 3.2 Hz and 1.5 Hz). A doublet at δ5.81 and three double doublets at δ5.61, 5.49 and 5.63 were assigned, respectively, to H-2, H-3, H-4 and H-5 on the basis of their coupling constants. The positioning and stereochemical assignment of the H-2, H-3, H-4, H-5 and H-6 signals were also confirmed by double-irradiation experiments as described for compound **1**. From the above studies the structure of **2** appears to be similar to that of (+)-piperenol A-triacetate, i.e. 2,4,5-triacetoxy-1-benzoyloxy methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate. The second benzoyl group thus appears to be located at C-3 from comparison of its ^1H NMR with that of (+)-piperenol A and its triacetate [2]. The absolute configuration of **2** was confirmed when its ^1H and ^{13}C NMR data were compared with that of (+)-piperenol A-triacetate prepared from piperenol A; it was found to be similar in all respects. Therefore, **2** is assigned the structure (+)-(2*S*,3*R*,4*R*,5*R*)-2,4,5-triacetoxy-1-benzoyloxy-methylcyclohex-1(6)-ene-2,3,4,5-tetrol-3-benzoate, designated (+)-piperenol A-triacetate.

One of the two other minor compounds also isolated was assigned the structure **3** on the basis of its spectral data. It was identified as (−)-kadsurin A, a neolignan. Kadsurin A was isolated by Tyagi *et al.* [3] from *P. schmiditi*. This, therefore, is the second report of its occurrence from a natural source.

The other minor neolignan belonging to the same class was assigned structure **4** on the basis of spectral measurements. It was identified as piperenone, previously reported by Matsui *et al.* [4] from *P. futokadsura*. As ^{13}C NMR data of **4** have not previously been reported, we have incorporated the assignment of its carbon signals (see Experimental).

EXPERIMENTAL

Mps: uncorr. IR: KBr. UV: MeOH ^1H NMR recorded at 90, 250, 400 and 500 MHz, ^{13}C NMR at 126, 100 and 63 MHz, with TMS as int. standard. The frs from the petrol extract of *P. cubeb* after further exhaustive CC yielded several minor compounds, four of which (**1**–**4**) were investigated further.

Piperenol C (**1**). Semi-solid $[\alpha]_D^{25}$ −40.0° ($CHCl_3$; *c* 0.2). Analysed for $C_{22}H_{24}O_{10}$ (found: C, 58.72, H, 5.37 requires C, 58.92, H, 5.39%). UV λ_{max}^{MeOH} 228, 274, 282 nm. IR ν_{max}^{KBr} cm^{-1}: 1720, 1600, 1580, 1450, 1351, 1314, 1279, 1170, 1050, 1020, 720. MS (*m/z* rel. int.): $[M]^+$ 448 (7), 388 (22), 327 (1), 304 (2), 288 (26), 244 (26), 207 (5), 165 (18), 122 (100). ^1H NMR ($CDCl_3$) δ: 1.98, 2.02, 2.08 and 2.12 (12H, 4 × *s*, 4 × OAc), 4.76 (1H, *dd*, J = 12.5 Hz, 0.8 Hz, H-7a), 5.06 (1H, *dd*, J = 12.5 Hz, 0.5 Hz, H-7b), 5.68 (1H, *d*, J = 7.4 Hz, H-2), 5.80 (1H, *dd*, J = 2.7 Hz, 0.3 Hz, H-3), 5.90 (1H, *dd*, J = 0.3 Hz, 2.7 Hz, H-4), 5.94 (1H, *dd*, J = 2.7 Hz, 3.7 Hz, H-5), 6.13 (1H, *dd*, J = 3.7 Hz, 0.5 Hz, H-6), 7.42–7.52 (3H, *m*, Ar, H-3′, 4′, 5′), 8.0–8.1 (2H, *m*, Ar, H-2′, 6′).

Piperenol A-triacetate (**2**). Crystalline solid mp 118–119°. $[\alpha]_D^{25}$ +17.5° ($CHCl_3$; *c* 1.10). Analysed for $C_{27}H_{26}O_{10}$ (found: C, 61.05, H, 4.84 requires C, 61.50, H, 4.97%). UV λ_{max}^{MeOH} 228, 270, 280 nm, IR ν_{max}^{KBr} (cm^{-1}); 2934, 1720, 1600, 1583, 1450, 1352, 1315, 1270, 1175, 1060, 1028, 720. MS (*m/z* rel. int.): $[M]^+$ 510 (21), 451 (37), 389 (1), 346 (2), 286 (82), 268 (13), 244 (100), 207 (8), 165 (13), 122 (15). ^1H NMR ($CDCl_3$): δ2.07, 2.11 and 2.16 (9H, 3 × *s*, 3 × OAc), 4.84 (1H, *dd*, J = 14.3 Hz, 1.5 Hz, H-7a), 4.88 (1H, *dd*, J = 14.3 Hz, 0.8 Hz, H-7b), 5.49 (1H, *dd*, J = 2.5 Hz, 6.5 Hz, H-4), 5.61 (1H, *dd*, J = 2.5 Hz, 5.1 Hz, H-3), 5.63 (1H, *dd*, J = 3.2 Hz, 6.5 Hz, H-5), 5.81 (1H, *d*, J = 5.1 Hz, H-2), 6.12 (1H, *dd*, J = 1.5 Hz, 3.2 Hz, H-6), 7.45–7.57 (6H, *m*, Ar, H-3′ and 3″, 4′ and 4″, 5′ and 5″) 7.94–8.01 (4H, *m*, Ar, H-2′ and 2″, 6′ and 6″). ^{13}C NMR ($CDCl_3$): δ134.1 (C-1), 70.1 (C-2), 69.6 (C-3), 68.2 (C-4), 67.4 (C-5), 126.9 (C-6), 64.0 (C-7), 129.2 and 129.6 (C-1′ and 1′), 129.7 and 129.8 (C-2′, 2″ and C-6′, 6″), 128.4 and 128.5 (C-3′ and 3″, C-5′ and 5″), 133.3 and 133.5 (C-4′, 4″), 165.3 and 165.8 (C=O), 169.7, 170.0 and 170.1 (3 × CO), 20.7, 20.8 and 20.9 (3 × $OCO\underline{C}H_3$).

Kadsurin A (**3**). Oil. $[\alpha]_D^{25}$ −102.1° ($CHCl_3$; *c* 0.51). Analysed for $C_{21}H_{24}O_6$ (found: C, 67.57, H, 6.47 requires C, 67.72, H, 6.49%). UV λ_{max}^{MeOH} 286 nm. IR ν_{max}^{KBr} cm^{-1}; 2934, 1687, 1642, 1608, 1514, 1480, 1310, 1252, 1110, 1028, 918, 858, 750. MS (*m/z* rel. int.): $[M]^+$ 372 (3), 210 (82), 179 (28), 165 (15), 162 (50), 151 (100), 138 (11), 135 (13). ^1H NMR ($CDCl_3$): δ0.98 (3H, *d*, J = 7.0 Hz, H-9′), 2.62 (1H, *d*, J = 16.5 Hz, H-5a), 2.88 (1H, *m*, H-8′), 3.10 (2H, *d*, J = 6.5 Hz, H-7), 3.28 (1H, *d*, J = 16.5 Hz, H-5b), 3.38 (3H, *s*, OMe-3), 3.50 (3H, *s*, OMe-4), 4.08 (1H, *d*, J = 10.8 Hz, H-7′), 5.04–5.28 (2H, *m*, H-9), 5.65–5.95 (1H, *m*, H-8), 5.95 (2H, *s*, O–CH_2–O), 6.44 (1H, *s*, H-2), 6.64–6.96 (3H, *m*, Ar, H-2′, 5′, 6′). ^{13}C NMR ($CDCl_3$): δ143.0 (C-1), 138.5 (C-2), 81.7 (C-3), 101.9 (C-4), 43.1 (C-5), 194.1 (C-6), 33.3 (C-7), 134.6 (C-8), 117.3 (C-9), 48.9 (OMe-3), 52.3 (OMe-4), 133.8 (C-1′), 107.8 (C-2′), 147.9 (C-3′), 147.5 (C-4′), 107.8 (C-5′), 121.0 (C-6′), 85.3 (C-7′), 48.9 (C-8′), 9.1 (C-9′), 100.9 (–OCH_2O–).

Piperenone (**4**). Crystalline solid, mp 87–89°; lit. [4] mp 86–87°. $[\alpha]_D^{25}$ −101° ($CHCl_3$; *c* 0.50). Analysed for $C_{22}H_{28}O_6$ (found: C, 68.0, H, 7.19 requires C, 68.02, H, 7.26%). UV λ_{max}^{MeOH} 231, 280, 285 nm. IR ν_{max}^{KBr} cm^{-1}: 2934, 2687, 1642, 1608, 1514, 1490, 1310, 1252, 1110, 1025, 918, 858, 780. MS (*m/z* rel. int.): $[M]^+$ 388 (100), 347 (40), 210 (6), 179 (12), 178 (72), 166 (8), 152 (8), 151 (67),138 (9.3).

^{1}H NMR ($CDCl_3$): δ0.98 (3H, *d*, J = 7.0 Hz, H-9′), 2.69 (1H, *d*, J = 16.8 Hz, H-5a), 2.89 (1H, *m*, H-8′), 3.16 (2H, *d*, J = 7.2 Hz, H-7), 3.29 (1H, *d*, J = 16.8 Hz, H-5b), 3.38 (3H, *s*, OMe), 3.51 (3H, *s*, OMe), 4.12 (1H, *d*, J = 11.0 Hz, H-7′), 5.11–5.17 (2H, *m*, H-9), 5.8–6.0 (1H, *m*, H-8), 3.85 and 3.86 (6H, *s*, 2 × Ar-OMe), 6.45(1H, *s*, H-2), 6.7–6.9 (3H, *m*, Ar-H, 2′, 5′, 6′). ^{13}C NMR ($CDCl_3$): δ142.9 (C-1), 138.3 (C-2), 81.6 (C-3), 101.7 (C-4), 42.9 (C-5), 193.0 (C-6), 33.1 (C-7), 134.3 (C-8), 117.2 (C-9), 48.7 (OMe-3), 52.2 (OMe-4), 131.9 (C-1′), 109.3 (C-2′), 148.8 (C-3′), 148.7 (C-4′), 110.2 (C-5′), 119.8 (C-6′), 85.2 (C-7′), 48.6 (C-8′) 9.9 (C-9′), 55.52 and 55.36 (2 × OCH_3).

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