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NEW BENZYLDIHYDROCHALCONES FROM *UVARIA CHAMAE*

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Key Word Index—*Uvaria chamae*; Annonaceae; benzyldihydrochalcones; chamuvarin; chamuvaritin; benzyl-benzoate.

Abstract—Two new benzyldihydrochalcones have been identified in the roots of *Uvaria chamae*. They are accompanied by the known benzyl benzoate.

INTRODUCTION

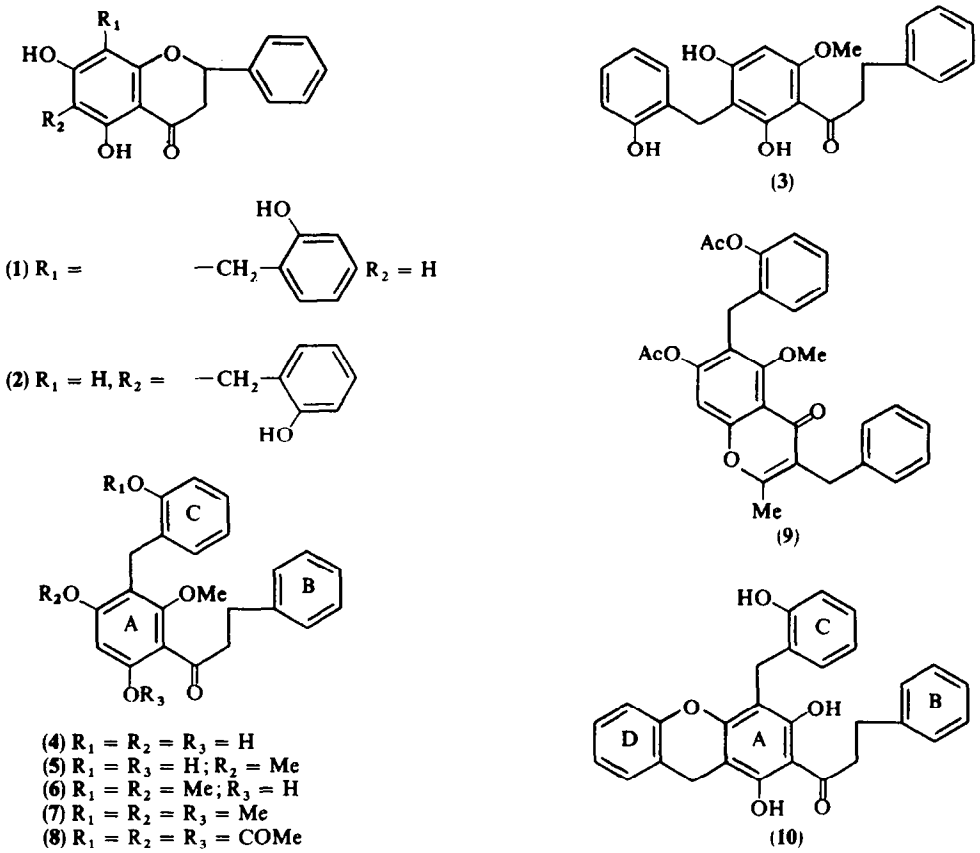
Uvaria chamae P. Beauv. is a small tree which grows in the tropical rain forest zone of West Africa stretching from Senegal to Zaire [1]. The roots of the plant are said to have purgative and febrifugal properties. A decoction of the root and rootback are drunk for fever and severe abdominal pains [2]. In continuation of our investigation of medicinal plants of Nigeria, we have examined the stem, stembark, leaves roots and rootbark of *U. chamae*. The recent report [3] of the isolation of two new *C*-benzylflavanones, uvaretin and isouvaretin (**1** and **2**) from *U. chamae* has prompted us to publish our own results. We now report on the chemical examination of the roots which gave two new benzyldyhydrochalcones chamuvarin (**4**) and chamuvaritin (**10**) and benzyl benzoate.

RESULTS

Hot hexane extraction of the roots of *U. chamae* from Oyo, Nigeria afforded a gum which was chromatographed on silica gel using increasing percentages of Et_2O in petrol to give three compounds. The first, an oil MS gave MW 212 analysing for $C_{14}H_{12}O_2$ was found to be benzyl benzoate by detailed examination of IR, NMR, MS Spectral data and by comparison with an authentic sample. The third compound, mp 164–165° MS gave MW 378 accounting for the formular $C_{23}H_{22}O_5$, was named chamuvarin. It gave a positive $FeCl_3$ test indicating the phenolic nature and a negative Shinoda reaction [4] suggesting absence of flavone or flavonone nucleus. IR showed bands at ν_{max} 3350 and 3250 cm^{-1} attributeable to phenolic hydroxy groups; a carbonyl absorption at 1630 cm^{-1} suggestive of the presence of *o*-hydroxy-ketone, 1600 indicative of aromatic ring. UV: λ_{max} 335*sh*, 293 and 237 nm (log ε = 3.21, 4.24 and 3.93 respectively) in agreement with the presence of a chalcone skeleton [5] in chamuvarin. The NMR spectrum (Varian T-60, Acetone-d_6, δ-scale) showed two two-proton signals of an A_2B_2 system centred at 3.05 and 3.35; a three-proton singlet at 3.82 (—OMe); a two-proton singlet at 3.90, one proton singlet at 6.2, a four proton multiplet near 6.90 and a five proton singlet at 7.22. It also showed two one-proton broad singlets at 7.32 and 7.40 (both lost on deuteration) assignable to phenolic —OH and a one proton sharp singlet at 14.73 (exchangeable with D_2O) attributeable to a hydrogen bonded phenolic —OH. The three —OH groups, —OMe and the carbonyl account for all the oxygens present. The absence of an ABX pattern with the X portion centred around 5.6 which is characteristic of the protons at H-3 and H-2 of a flavanone nucleus [3] such as in (**1**) confirmed that chamuvarin was not a flavanone. Furthermore the absence of an AB quartet J = 16 Hz for the —HC=CH— protons between 7.3 and 8.5 which is characteristic [6, 7] for the ArCH=CH—CO—Ar system in chalcones confirmed it was not a chalcone. The A_2B_2 pattern was suggestive of a β-propiophenone fragment [8] such as is present in dihydrochalcones.

The hydrogen-bonded phenolic —OH at 14.73 in the NMR would then be placed in the C-2′ position, making chamuvarin a 2′-hydroxy-dihydrochalcone. This was confirmed by the fact that chamuvarin smoothly underwent the Kostanecki reaction [10] (see later). The B ring must be unsubstituted [3] to account for the 5H(*s*) at 7.28. The presence of four aromatic protons as 4H(*m*) meant the presence of another benzene ring (ring C), which must carry two substituents one of them being either an —OMe or —OH and the other a carbon chain linking it to the ring A or the dihydrochalcone. The two substituents must be *ortho* to each other, since any other relationship would have led to different absorption patterns. The singlet nature of the 2H absorption at 3.90 meant the absence of protons on adjacent carbons. The absorption could then be either an Ar—CH_2OH or Ar—CH_2—Ar. The former was ruled out because on acetylation of chamuvarin (see later) the 3.90 peak suffered no shift. The chemical shift is characteristic [3, 8] of Ar—CH_2—Ar fragment. Ring C is thus an *o*-hydroxy or methoxy benzyl group.

The —OH groups were located as follows. The chelated —OH had earlier on been placed at C-2′ position. Since the NMR of chamuvarin showed only one sharp signal at 14.73, it became clear that only one —OH was *ortho* to the carbonyl group. If there were two *o*-—OH groups a less sharp peak in the region or 10.4–11.7 would have resulted as in phloroacetophenone derivatives [11]. The —OMe is thus in C-6′ in ring A. The appearance of the one aromatic proton singlet at 6.2 indicates [6] that it is located between two oxygens, either between the —OMe at C-6′ and an —OH in C-4′ or between the chelated —OH at C-2′ and an —OH



Scheme 1.

in C-4′. This places the second —OH at C-4′ and therefore the third —OH must be on the benzyl ring C. Chamuvarin thus possesses an *o*-hydroxybenzyl substituent which is attached to the dihydrochalcone ring A at either C-3′ or C-5′. Attachment at C-3′ would make it identical with another uvaretin, a 3′-benzyldihydrochalcone recently isolated from *U. acuminata* whose structure was found [8] to be (3) by a combination of spectral data and X-ray crystallography. That chamuvarin was not the new uvaretin (3) followed from comparison of detailed IR, NMR, UV spectral data and mp [8, 9]. The structure is therefore (4). Confirmation of this structure followed from the reactions discussed below.

Methylation with ethereal CH_2N_2 afforded a monomethyl ether (5) mp 132–134° which still showed a chelated —OH absorption at 15.1 in the NMR. The mp and spectral data were different from those of uvaretin monomethyl ether [8]. Furthermore, methylation with dimethyl sulphate in KOH furnished a dimethyl ether mp 125–137°, still showing a chelated —OH and therefore has structure (6) whose spectral data and mp differed from those of uvaretin dimethyl ether [8]. Treatment of chamuvarin with excess ethereal CH_2N_2 resulted in complete methylation furnishing the trimethyl ether (7) mp 79–81°. On acetylation with Ac_2O–Py, chamuvarin gave a triacetate (8) mp 106–108. The NMR of the triacetate showed that the one-proton singlet at 6.20 had moved to 6.65 confirming that this proton was between two —OH groups.

Chamuvarin on refluxing with fused NaOAc in Ac_2O, underwent the Kostanecki reaction [10] characteristic of 2′-hydrpxydihydrochalcones [12] to give a compound whose spectral data were in agreement with the chromene (9). The NMR of (9) lacked the two 2H signals of the A_2B_2 system centred at 3.05 and 3.35. This compound could not be made to crystallize, but was homogenous on TLC. When it was passed through a short column of alumina to further purify it, the resulting oil crystallized. IR now showed a peak at 3350 cm^{-1} indicating presence of —OH and suggesting the loss of an —OAc group. A similar loss of an acetoxy group was observed when the Kostanecki reaction product of uvaretin was passed through a similar column [8]. The compound was found to be insoluble in most solvents and the NMR could not be taken in Py-d_5 for direct comparison.

The second compound had mp 152–155° and was named chamuvaritin; MW, 452 and elemental analysis gave a formula $C_{29}H_{24}O_5$. IR ν_{max} 3450, 3250, 1630, 1600 cm^{-1} attributeable to phenolic —OH, chelated —OH, H-bonded aromatic CO and aromatic ring respectively. It also gave a positive $FeCl_3$ and negative Shinoda reaction [4]. UV: λ_{max} 285*sh*, 302, 340 nm (log ε = 3.97, 4.08 and 3.45 respectively) suggested the presence of dihydrochalcone system just as in chamuvarin. Confirmation followed from the NMR spectrum (Varian T-60, Acetone-d_6) which had the A_2B_2 pattern characteristic of β-propiophenone moiety as two two-proton signals centred at 3.10 and 3.56. The NMR was similar

to that of chamuvarin in having a 2H(*s*) at 3.96, assignable to benzylic methylene; 4H (*m*) centred at 7.0 reminiscent of ring C aromatic protons of an *o*-hydroxy benzylic group; 5H(*s*) at 7.30 which was characteristic of an unsubstituted ring B; two 1H broad singlets at 7.10 and 7.34 which were exchangeable with D_2O and a sharp IH(*s*) at 14.30 which disappeared on deuteration indicating the presence of three phenolic —OH groups one of which was chelated. Acetylation with Ac_2O–Py (see later) afforded a triacetate in which the chelated —OH had been lost, confirming the presence of three —OH. NMR spectrum of chamuvaritin however lacked any —OMe peak and the 1H(*s*) at 6.2 which was assigned to C-3′ proton in chamuvarin. That chamuvaritin contained another ortho substituted benzylic fragment (ring D) was evident from the NMR which showed another 4H(*m*) at 7.24 for the aromatic protons; and another 2H(*s*) at 3.84, for the benzylic methylene.

Of the five oxygens, four have so far been accounted for in the presence of β-propiophenone and three —OH groups. Two of the —OH groups have been placed in the C-2′ position in ring A and on ring C. Since the orthohydroxybenzyl ring C must be at C-5′ by comparison with chamuvarin, (**4**) the third —OH would then be located at C-3′, C-4′ or C-6′ on ring A. Considering the molecular formular of chamuvaritin, the only atom unaccounted for is the fifth oxygen atom which must therefore be present only as an oxygen bridge linking ring D with ring A. Since the oxygen bridge is ortho to the benzyl group of ring D, the position of the third —OH would obviously be C-6′. By comparing chamuvarin and chamuvaritin the xanthene structure (**10**) was proposed for chamuvaritin.

The NMR of chamuvaritin triacetate showed the three —OCOMe groups as 3H(*s*) at 2.0, 2.2 and 2.36. When these are compared with those of chamuvarin triacetate (**8**) which resonate at 2.0, 2.1 and 2.36 it became obvious that two of the acetates were in the same positions in both compounds while the third were not, thus confirming the location of the —OH groups in chamuvaritin and hence the structure (**10**).

The syntheses of both compounds are being carried out and will be reported later.

EXPERIMENTAL

Unless otherwise specified UV spectra were taken in EtOH, IR spectra were in Nujol and NMR spectra were recorded on Varian T-60 in $CDCl_3$ as solvent with TMS as internal standard. Si gel refers to Merck Kieselgel 60 (70–230 mesh ASTM).

Extraction of the roots. Powdered roots or *Uvaria chamae* (2.2 kg) were extracted with hexane. The concn gave a gum (25 g) which was dissolved in C_6H_6 and chromatographed on a column of Si gel (200 g) eluting with increasing percentages of Et_2O–petrol (60–80°). Petrol–Et_2O (9:1) eluted phenyl benzoate (3.2 g). Petrol–Et_2O (4:1) fractions furnished chamuvaritin (**10**) as light yellow crystals mp 152–155° (0.3 g). UV: λ_{max} (log ε) 285*sh* (3.97), 302 (4.08), 340 (3.45) nm; IR: ν_{max} 3450, 3250, 1630, 1600, 1565, 1455, 1370, 1325, 1260, 1215, 1200, 1140, 1105, 890, 815, 755, 745, 720 cm^{-1}. NMR: (Me_2CO–d_6) δ 14.30 (1H, *s*, disappearing with D_2O, ArOH) 7.34 (1H, *br*, *s*, lost on deuteration, ArOH), 7.30 (5H, *s*, ArH), 7.24 (4H, *m*, ArH) 7.10 (1H, *br s*, lost deuteration, ArOH), 7.0 (4H, *m*, ArH) 3.96 (2H, *s*, Ar—CH_2—Ar, 3.84 (2H, *s*, Ar—CH_2—Ar), 3.56, 3.10 (each 2H, A_2B_2 pattern); MS: *m/e* 452 (M^+ base), 347, 320, 253, 241, 107 and 91. (Found: C, 76.96; H, 5.52; $C_{29}H_{24}O_5$ requires: C, 76.97; H, 5.35%). Petrol–Et_2O (7:3) eluates afforded chamuvarin (**4**) as white crystals mp 164–165° (1.4 g). UV: λ_{max} (log ε) 335 (*sh* 3.21), 293 (4.24), 237 (3.93) nm; IR ν_{max} 3350, 3250, 1630, 1600, 1495, 1460, 1360, 1300, 1235, 1200, 1135, 1100, 1010, 975, 915, 862, 800, 780, 760, 755 cm^{-1}. NMR: (Me_2CO-d_6) δ 14.73 (1H, *s*, lost on deuteration, ArOH), 7.40, 7.32 (each 1H, *br s*, exchangeable with D_2O, ArOH), 722 (5H, *s*, ArH) 6.90 (4H, *m*, ArH), 6.2 (1H, *s*, ArH), 3.90 (2H, *s*, Ar—CH_2—Ar), 3.82 (3H, *s*, ArOMe), 3.35, 3.05 (each 2H, A_2B_2 pattern); MS: *m/e* 378 (M^+ base), 359, 273, 246, 179, 167, 140, 107 and 91. (Found: C, 73.10; H, 5.86; $C_{23}H_{22}O_5$ requires: C, 73.00; H, 5.86%).

Chamuvarin monomethylether (**5**). Chamuvarin (0.08 g) was dissolved in minimum quantity of dry MeOH and dry Et_2O (30 ml) added. Ethereal CH_2N_2 was passed into it for 1 hr. Mixture was left in the freezer (−5°) for 48 hr. It was then worked up in the usual manner to give crude chamuvarin monomethylether (0.072 g). This was passed through a column of Si gel and crystallized from C_6H_6/hexane as light yellow plates mp 132–134°. UV: λ_{max} (log ε) 292 (3.90) nm. IR: ν_{max} 3400, 1630, 1595, 1460, 1375, 1240, 1175, 1110, 1015, 925, 787 cm^{-1}. NMR: δ 15.1 (1H, *s*, disappears with D_2O, ArOH), 7.45 (1H, *br*, lost on deuteration, ArOH), 7.3 (5H, *s*, ArH), 6.96 (4H, *m*, ArH), 6.02 (1H, *s*, ArH), 4.0 (3H, *s* ArOMe), 3.9 (5H, *s*, ArOME and Ar—CH_2—Ar), 3.36, 3.10 (each 2H, A_2B_2 pattern); MS: *m/e* 392 (M^+ base), 287, 260, 193, 181, 154, 121, 107 and 91. (Found: C, 73.23; H, 6.29, $C_{24}H_{24}O_5$ requires: C, 73.45; H, 6.16%).

Chamuvarin dimethyl ether (**6**). Me_2SO_4 and 40% aq. soln of KOH were added in small portions alternatively and with stirring to a soln of chamuvarin (0.2 g) in MeOH (3 ml) and KOH (0.2 g) at room temp. over 15 min. Sitrring was continued for another 1 hr. Mixture was acidified with dil. HCl and extracted (2 × 50 ml) with Et_2O. Combined Et_2O extracts was washed, dried and evapd to a gummy solid (0.18 g). This was passed through a column of Si gel and crystallized from C_6H_6/hexane as plates mp 125–127° of chamuvarin dimethyl ether. UV: λ_{max} (log ε) 280 (3.53), 318 (3.73), IR: ν_{max} 3450, 1620, 1580, 1470, 1415, 1375, 1235, 1220, 1205, 1125, 1110, 1030, 780, 750, 715 cm^{-1}: NMR: δ 13.8 (1H, *s*, disappears with D_2O, ArOH), 7.32 (5H, *s*, ArH) 6.85 (4H, *m*, ArH), 6.05 (1H, *s*, ArH), 3.98 (2H, *s*, Ar—CH_2—Ar), 3.90 (6H, *s*, ArOMe), 3.80 (3H, *s*, ArOMe), 3.34, 3.05 (each 2H, A_2B_2 pattern); MS: *m/e* 4·6 (M^+), 329, 301 274, 193, 181, 166, 121 (base) 91, 77, 65. (Found: C, 74.01; H, 6.42; $C_{25}H_{26}O_5$ requires: C, 73.86; H, 6.45%).

Chamuvarin trimethyl ether (**7**). Chamuvarin (0.2 g) dissolved in a minimum amount of MeOH and dry Et_2O (40 ml) was treated with ethereal CH_2N_2 at 0° for 2 hr. After standing at room temp. for 4 hr it was worked up in the usual manner to give chamuvarin trimethyl ether (0.16 g), which was recrsytallized from Me_2CO furnishing long colourless needles mp 79–81°. UV: λ_{max} (log ε) 291 (3.80) nm; IR; ν_{max} 1690, 1595, 1460, 1375, 1295, 1240, 1175, 1115, 1085, 1045, 970, 945, 915, 870, 790 cm^{-1}. NMR: δ 7.23 (5H, *s*, ArH, 6.90 (4H, *m*, ArH), 6.0 (1H, *s*, ArH), 3.95 (3H, *s*, ArOMe, 3.88 (3H, *s*, ArOMe, 3.85 (3H, *s*, ArOME), 3.82 (3H, *s*, ArOMe), 3.75 (2H, *s*, Ar—CH_2—Ar), 3.3, 3.02 (each 2H, A_2B_2 pattern). MS: *m/e* 420 (M^+), 406, 392, 301, 287, 260, 193 (base 181, 154, 107 and 91 (Found: C, 74.40; H, 6.91; $C_{26}H_{28}O_5$ requires: C, 74.26; H, 6.71%).

Chamuvarin triacetate (**8**). Crystallized from EtOAc–hexane as plates, mp 106–108°. UV: λ_{max} (log ε) 280 (3.32), 300 (3.43) nm. IR: ν_{max} 1760, 1745, 1690, 1600, 1570, 1450, 1375, 1290, 1225, 1160, 1110, 1070, 1040, 1010, 920, 885, 870, 825, 792, 740 cm^{-1} NMR: δ 7.28 (5H, *s*, ArH), 7.1 (4H, *m*, ArH), 6.65 (1H, *s*, ArH), 3.78 (3H, *s*, ArOMe), 3.65 (2H, *s*, Ar—CH_2—Ar), 3.18, 3.02 (each 2H, A_2B_2 pattern), 2.36 (3H, *s*, ArOAc), 2.1 (3H, *s*, ArOAc), 2.0 (3H, *s*, ArOAc). MS: *m/e* 504 (M^+) 462, 421, 359, 315, 273, 179 (base), and 91. (Found: C, 68.87; H, 5.53; $C_{29}H_{28}O_8$ requires: C, 69.04; H, 5.59%).

Kostanecki reaction product (**9**). Chamuvarin (0.085 g) was treated with Ac_2O (2 ml) and NaOAc (0.2 g) and refluxed at 160° for 20 hr. Cooled to room temp., poured into H_2O and extracted with Et_2O (2 × 30 ml). Combined Et_2O fractions were washed, dried and evapd to an oil (0.079 g), which failed to crystallize, but was however homogenuous on TLC. UV: λ_{max} (log ε) 277, 318 (3.59 and 4.70 respectively) nm. IR: ν_{max} 1760, 1630, 1575, 1440, 1350, 1175, 1160, 1110, 1050, 1025 cm^{-1}.

NMR: δ 7.3 (5H, *s*, ArH), 7.12 (4H, *m*, ArH), 6.62 (1H, *s*, ArH), 3.98 (3H, *s*, ArOMe), 3.92 (2H, *s*, Ar—CH_2—Ar), 3.84 (2H, *s*, Ar—CH_2—Ar), 2.28 (3H, *s*, ArMe) 2,20 (6H, *s*, ArOAc). MS: *m/e* 486 (M^+). This oil was passed through a short column of Al_2O_3, eluting with Et_2O, then $CHCl_3$. Evaporation of the $CHCl_3$ extracts gave an oil which crystallized from MeOH–EtOAc mp 249–251°. The compound had lost one OAc group. IR: ν_{max} 3400 (free —OH) 1750, 1640, 1600, 1560, 1445, 1420, 1375, 1215, 1170, 1130, 1090, 1000, 830 cm^{-1}. UV. λ_{max}(log ε) 275, 280, 285, 295, 310, (3.50, 3.57, 3.61, 3.68 and 3.80) nm. MS: *m/e* 444 (M^+) (Found: C, 72.78; H, 5.45; $C_{27}H_{24}O_6$ requires: C, 72.96; H, 5.44%).

Chamuvaritin triacetate. Chamuvaritin was acetylated to give a light yellow oil which could not be made to crystallize, but was homogenuous on TLC. IR: ν_{max} (soln in $CHCl_3$) 1770, 1755, 1680, 1600, 1430, 1350, 1300, 1225, 1175, 1075, 1020, 900 cm^{-1}. NMR: δ 7.35 (5H, *s*, ArH), 7.2 (4H, *m*, ArH), 7.0 (4H, *m*, ArH), 3.82 (2H, *s*, Ar—CH_2—Ar), 3.7 (2H, *s*, Ar—CH_2—Ar), 3.35, 3.18 (each 2H, A_2B_2 pattern), 2.36 (3H, *s*, ArOAc), 2.2 (3H, *s*, ArOAc), 2.0 (3H, *s*, ArOAc). MS: *m/e* 578 (M^+), (Found: C, 72.47; H, 5.25; $C_{35}H_{30}O_8$ requires: C, 72.65; H, 5.23%).

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