Phytochemistry, 1978, Vol 17, pp 1814–1815 © Pergamon Press Ltd Printed in England 0031-9422/78/1001-1814 $02.00/0

# NEW ALKALOIDS FROM *AEGLE MARMELOS**

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(*Revised received* 20 *April* 1978)

**Key Word Index**—*Aegle marmelos*; Rutaceae; *O*-(3,3-dimethylallyl)-halfordinol; cinnamic acid amides; structural analysis; synthesis.

**Abstract**—Four new alkaloids, *O*-(3,3-dimethylallyl)-halfordinol, *N*-2-ethoxy-2-(4-methoxyphenyl)ethylcinnamamide, *N*-2-methoxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnamamide, and *N*-2-methoxy-2-(4-methoxyphenyl)-ethylcinnamamide have been isolated from the leaves of *Aegle marmelos* and their structural assignments confirmed by synthesis.

## INTRODUCTION

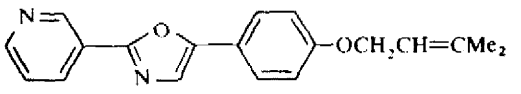
The leaves and fruits of *Aegle marmelos* Corr. (Rutaceae) have been widely prescribed in various intestinal ailments in the indigenous system of medicine. The results obtained for the isolation and characterization of the active principles from the leaves of the plant are described in the present communication.

## RESULTS AND DISCUSSION

The hexane soluble fraction of the MeOH–EtOH extracts of the leaves of *A. marmelos* on column chromatography over neutral $Al_2O_3$ yielded alkaloids A, B, C, and D.

Alkaloid A, mp 115°, $C_{19}H_{18}N_2O_2$, $M^+$, 306, showed UV absorbance at $\lambda_{max}^{MeOH}$ 248 (log $\varepsilon$ 4.10), 255 (4.03) and 325 nm (4.50) which remained unaffected by the addition of alkali. The characteristic IR bands at $\nu_{max}^{KBr}$ 1625, 1580 and 1110 $cm^{-1}$ indicated the presence of a 1,4-disubstituted benzene ring, trisubstituted olefin and ether linkage, respectively. A 3,3-dimethylallyloxy chain could easily be identified from the PMR spectrum which showed resonances at $\tau$ 8.22 (*bs*, 6H, $=C(C\underline{H}_3)_2$), 5.47 (*d*, 2H, $OC\underline{H}_2$) and 4.52 (*t*, 1H, $C=C\underline{H}$), respectively. A pair of doublets showing an $A_2B_2$ system at $\tau$ 3.12 and 2.42 ($J$ = 8.5 Hz) confirmed the 1,4-disubstituted benzene ring. The chemical shift and multiplicity of the rest of the proton signals in the spectrum were identical to those reported for nicotinamide [1] and thus suggested a pyridine residue in the molecule.

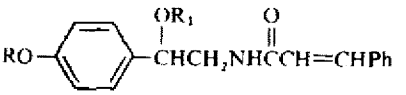
The MS of alkaloid A showed a conspicuous $M^+$ at *m/e* 306 with a base peak at *m/e* 238 due to the ion ($M^+$-side chain). The rest of the fragmentation pattern was similar to halfordinol [2, 3]. On the basis of above evidence, the alkaloid A could be identified as *O*-(3,3-dimethylallyl)halfordinol [4] (1) and the assignment was confirmed by synthesis. Thus, the condensation of 3,3-dimethylallyl bromide with halfordinol furnished a product identical in all respects with the alkaloid A.




(1)

The alkaloid B, mp 99–101°, $C_{20}H_{23}NO_3$, $M^+$, 325, exhibited UV absorbance at $\lambda_{max}^{EtOH}$ 218 (log $\varepsilon$ 4.08), 224 (4.08) and 275 nm (4.1), indicative of a *trans* cinnamamide group. The IR spectrum revealed the presence of NH (3340 $cm^{-1}$) and bands at 1648 and 1605 $cm^{-1}$ were diagnostic of the *trans* conjugation. Its PMR spectrum showed two doublets of one proton each at $\tau$ 3.52 and 2.43 ($J$ = 16 Hz) for olefinic protons and a multiplet centred around $\tau$ 2.52–2.95 for 9 aromatic protons. The ABX pattern of the benzylic methine appeared as two sets of doublets spread over from $\tau$ 5.5–5.64. A multiplet between $\tau$ 6.05–6.54 partly obscured by a methoxy signal ($\tau$ 6.24) was assigned to methylene protons adjacent to the benzylic carbon. A triplet at $\tau$ 8.85 ($J$ = 8 Hz) and a deformed quartet at $\tau$ 6.68 accounted for an ethoxy function. The alkaloid B was, therefore, formulated as *N*-2-ethoxy-2-(4-methoxyphenyl)ethylcinnamamide (2) and its structure was confirmed by synthesis. The 4-methoxy-$\omega$-nitrostyrene obtained by conventional methods was converted to $\alpha$-ethoxy-$\beta$-nitroethyl-4-methoxybenzene under Michael conditions which on reduction with $LiAlH_4$ afforded $\beta$-ethoxy-$\beta$-(4-methoxyphenyl)ethylamine. The latter on reaction with cinnamoyl chloride yielded a product, identical in all respects with alkaloid B.

The alkaloid C, mp 110°, $M^+$, 365, analysed for $C_{23}H_{27}NO_3$. Its spectral studies suggested a close analogy with the alkaloid B except for the presence of a methoxy instead of an ethoxy function at the benzylic carbon and a 3,3-dimethylallyloxy group in place of the methoxy function at $C_4$ of the phenyl ring. It was, therefor , formulated as *N*-2-methoxy-2-[4-(3'3'-dimethylallyloxy) phenyl] ethylcinnamamide (3).




| | R | $R_1$ |
|---|---|---|
| (2) | Me | Et |
| (3) | $CH_2CH=CMe_2$ | Me |
| (4) | Me | Me |
| (5) | Me | H |

The alkaloid D, mp 135°, $C_{19}H_{21}NO_3$, $M^+$, 311, had spectral properties identical with those of alkaloid C with the exception of it being a methyl rather than a

* CDRI Communication No. 2405.

3,3-dimethylallyl ether. It could, therefore be represented as *N*-2-methoxy-2-(4-methoxyphenyl) ethylcinnamamide (**4**).

The isolation of alkaloids (**1**), (**2**), (**3**) and (**4**) in the present study and that of halfordinol [2] and aegeline [5] (**5**) in earlier reports, raised the possibility that artefact formation was occurring during isolation. A solution of (**1**) in N HCl kept at room temperature for 5 min on work-up gave a quantitative yield of halfordinol, thus indicating that the latter was an artefact of (**1**). Similarly, a change from MeOH to EtOH as extraction solvent during the isolation of (**4**) resulted in our obtaining (**2**) instead of (**4**); thus indicating that (**2**) and (**4**) were both artefacts of aegeline.

## EXPERIMENTAL

All mps are uncorr. The PMR spectra were recorded at 60 MHz using TMS as an internal standard. The MS were recorded on a mass spectrometer fitted with a direct inlet system.

*Isolation of alkaloids.* Fresh leaves of *A. marmelos* (10 kg) were percolated with MeOH. The residue obtained after removal of the solvent was diluted with $H_2O$, steam distilled and extracted with hexane (4 × 500 ml). The hexane extract on concn left a residue (30 g) which was chromatographed on a column of neutral $Al_2O_3$ (1.5 kg) in hexane and eluted with increasing proportions of $C_6H_6$ followed by EtOAc.

O-3,3-(*Dimethylallyl*)*halfordinol* (**1**) (450 mg) was eluted with $C_6H_6$ and crystallized from a mixture of $C_6H_6$–hexane, mp 115° and analysed for $C_{19}H_{18}N_2O_2$, UV: $\lambda_{max}^{MeOH}$ nm: 248 (log ε 4.10), 255 (4.03), and 325 (4.50); IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3400, 2907, 1625, 1580, 1506, 1462, 1290, 1244, 1190, 1110, 1076, 899, 820, 803, 790, 725 and 702; PMR ($CCl_4$): τ 8.22 (*s*, 6H, $2CH_3$), 5.47 (*d*, 2H, $CH_2$, *J* = 7 Hz), 4.52 (*m*, 1H, C=CH); 3.12 and 2.42 (*d*, 2H each, ArH, *J* = 8.5 Hz), 2.75 (*s*, 1H, C-5H), 2.6 (*m*, 1H, C-3H), 1.79 (*m*, 1H, C-4H), 1.4 (*dd*, 1H, C-2H, *J* = 5 and 1.5 Hz) and 0.76 (*m*, 1H, C-1H); MS: *m/e* $M^+$ 306 (53%), 239 (70), 238 (100), 237 (40), 210 (53), 209 (30), 156 (36), 155 (46), 154 (46), 150 (20), 149 (60), 141 (14), 121 (25), 114 (20), 78 (29) and 71 (27).

Elution with $C_6H_6$ gave *N*-2-methoxy-2-[4-(3′,3′-dimethylallyloxy)phenyl] ethylcinnamamide (**3**) (330 mg), mp 110° (hexane–$C_6H_6$), which analysed for $C_{23}H_{27}NO_3$, UV $\lambda_{max}^{MeOH}$ nm: 217 (log ε 4.31), 224 (4.35) and 276 (4.38); IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3289, 2849, 1656, 1631, 1558, 1513, 1451, 1377, 1284, 1035, 767 and 723; PMR ($CDCl_3$): τ 8.24 and 8.2 (*bs*, 3H each, 2 × $CH_3$), 6.77 (*s*, 3H, $OCH_3$), 6.22 (*m*, 2H, $CH_2NH$), 5.8 (*m*, 1H, CH), 5.5 (*d*, 2H, $OCH_2$, *J* = 7 Hz), 4.52 (*m*, 1H, $(CH_3)_2$ C=CH—), 3.59 and 2.41 (*d*, 1H each, CH=CHAr, *J* = 16 Hz), 3.2 and 2.8 (*d*, 2H each, ArH, *J* = 8.5 Hz), and 2.6 (*m*, 5H, ArH); MS: *m/e* 365 ($M^+$), 333, 305, 295, 267, 238, 226, 205, 137, 131, 120, 103, 77 and 69.

Further elution with 5% EtOAc in $C_6H_6$ gave *N*-2-methoxy-2-(4-methoxyphenyl)ethylcinnamamide (**4**) (1.5 g), mp 135° (hexane–$C_6H_6$) which analysed for $C_{19}H_{21}NO_3$, UV $\lambda_{max}^{MeOH}$ nm: 217 (log ε 4.30), 223 (4.36) and 275 (4.39); IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3257, 2907, 1656, 1621, 1511, 1445, 1339, 1295, 1174, 1107, 1085, 768 and 711; PMR ($CDCl_3$): τ 6.74 (*s*, 3H, aliphatic $OCH_3$), 6.19 (*s*, 3H, Ar–$OCH_3$), 6.74–6.19 (*m*, 2H, $NCH_2$), 5.69 (*m*, 1H, CH), 3.7 and 2.41 (*d*, 1H each, CH=CHAr, *J* = 16 Hz), 3.2 and 2.8 (*d*, 2H each, ArH, *J* = 8 Hz) and 2.6 (*m*, 5H, ArH).

N-2-*Ethoxy*-2-(4-*methoxyphenyl*)*ethylcinnamamide* (**2**). The hexane soluble fraction (20 g) of the EtOH extract of the leaves (6 kg) was chromatographed on a column of neutral $Al_2O_3$ (1 kg). Elution with 10% EtOAc in $C_6H_6$ afforded (**2**) (2.4 g) mp 99–100° (hexane–$C_6H_6$) and analysed for $C_{20}H_{23}NO_3$, UV $\lambda_{max}^{EtOH}$ nm: 218 (log ε 4.08), 224 (4.08) and 275 (4.10); IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3340, 3040, 1684, 1648, 1605, 1541, 1361, 1269, 1192, 1112, 1045, 1000, 874, 771 and 720; PMR ($CDCl_3$): τ 8.85 (*t*, 3H, $CH_2CH_3$, *J* = 8 Hz), 6.68 (*q*, 2H, $CH_2CH_3$, *J* = 8 Hz), 6.54–6.05 (*m*, 2H, $CH_2$), 6.24 (*s*, 3H, $OCH_3$), 5.64–5.5 (*dd*, CH, $J_{AX}$ = 4 and $J_{BX}$ = 9 Hz), 3.52 and 2.43 (*d*, 1H each, CH=CH, *J* = 16 Hz) and 2.95–2.52 (*m*, 9H, ArH); MS: *m/e* 325 ($M^+$, 17%), 295 (5), 279 (5), 177 (80), 165 (100), 150 (21), 138 (41), 137 (96), 131 (64), 109 (65), 103 (60), 94 (48) and 77 (57).

*Synthesis of* O-(3,3-*dimethylallyl*)-*halfordinol* (**1**). A mixture of halfordinol (80 mg), anhydrous $Me_2CO$, 3,3-dimethylallyl bromide (0.5 ml) and anhydrous $K_2CO_3$ (1 g) was heated at 100° for 2 hr followed by refluxing for another 5 hr at 125°. It was cooled and filtered and the viscous residue obtained after removal of the solvent was chromatographed on a column of neutral $Al_2O_3$ (15 g). Elution with 5% EtOAc–$C_6H_6$ afforded (**1**) (26 mg) identical in all respects with the natural product.

*Synthesis of* N-2-*ethoxy*-2-(4-*methoxyphenyl*)*ethylcinnamamide* (**4**). A soln of 4-methoxy-ω-nitrostyrene (4 g) in EtOH (80 ml) was treated with NaOEt (prepared from Na metal (0.9 g) and EtOH (20 ml)). After addition of a few drops of HOAc, the reaction mixture was shaken for 30 min and poured onto $H_2O$ (50 ml) and extracted with $Et_2O$ (3 × 20 ml). The $Et_2O$ layer was washed with $H_2O$, dried ($Na_2SO_4$) and concd to give α-ethoxy-β-nitroethyl-4-methoxybenzene (3.3 g) as a viscous oil (Found: C, 58.55; H, 6.52; N, 6.02. $C_{11}H_{15}NO_4$ requires: C, 58.66; H, 6.66; N, 6.22%); PMR($CDCl_3$):τ 8.9 (*t*, 3H, $OCH_2CH_3$, *J* = 8 Hz), 6.59 (*q*, 2H, $OCH_2CH_3$, *J* = 8 Hz), 6.2 (*s*, 3H, $OCH_3$), 5.6–5.04 (*m*, 3H, CH—$CH_2NO_2$), 3.2 and 2.75 (*d*, 2H each, ArH, *J* = 9 Hz).

The preceding compound (3.3 g) in anhydrous $Et_2O$ (20 ml) was reacted with a suspension of $LiAlH_4$ (6 g) in dry $Et_2O$ to furnish β-ethoxy-β-(4-methoxyphenyl)ethylamine (2.2 g) (Found: C, 67.63; H, 8.61; N, 7, 07. $C_{11}H_{17}NO_2$ requires: C, 67.69; H, 8.71; N, 7.10%); PMR ($CDCl_3$): τ 8.89 (*t*, 3H, $OCH_2CH_3$, *J* = 8 Hz), 6.74 (*q*, 2H, $OCH_2CH_3$, *J* = 8 Hz), 6.29 (*s*, 3H, $OCH_3$), 7.25 (*bd*, 2H, $CH_2NH_2$), 5.92 (*m*, 1H, CH), 3.27 and 2.9 (*d*, 2H each, ArH, *J* = 9 Hz) and 8.25 ($NH_2$).

A mixture of the foregoing amine (1 g), cinnamoyl chloride (0.5 g), dry $C_6H_6$ (50 ml) and anhydrous $K_2CO_3$ (2 g) was refluxed at 100° for 6 hr. The reaction mixture was cooled, filtered and the filtrate was washed successively with dil HCl, NaOH and $H_2O$. The organic layer was dried ($Na_2SO_4$) and concd to give a residue which solidified on standing in hexane. It was recrystallized from hexane–$C_6H_6$, mp 98–99°, identical in all respects with the natural material.

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