Pergamon

PII: S0031-9422(96)00304-4

Phytochemistry, Vol. 43, No. 3, pp. 719–722, 1996

0031-9422/96 $15.00 + 0.00

QUINOLONE ALKALOIDS FROM *EVODIA RUTAECARPA*

YUAN-QING TANG, XIAO-ZHANG FENG and LIANG HUANG

Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing 100050, China

(*Received in revised form* 20 *March* 1996)

Key Word Index—*Evodia rutaecarpa*; Rutaceae; fruits quinolone alkaloids; 1-methyl-2-dodecyl-4(1H)-quinolone; 2-tridecyl-4(1H)-quinolone; 1-methyl-2-[(*Z*)-5-undecenyl]-4(1*H*)-quinolone; 1-methyl-2-[(*Z*)-9-pentadecenyl]-4(1*H*)-quinolone; 1-methyl-2-[(*Z*)-7-tridecenyl]-4(1*H*)-quinolone.

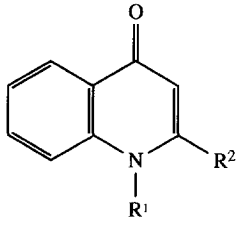
Abstract—Five new quinolone alkaloids were isolated from the fruits of *Evodia rutaecarpa*, together with seven known ones. Their structures were determined on the basis of spectral data and chemical reactions. Copyright © 1996 Published by Elsevier Science Ltd

INTRODUCTION

The fruit of *Evodia rutaecarpa*, a Chinese traditional drug (Wu-Chu-Yu), has been used in the treatment of headache, abdominal pain, dysentery, postpartum haemorrhage, amenorrhea, chill limbs, migraines and nausea [1]. The presence of indole alkaloids [2–9], quinolone alkaloids [10, 11], limonoids [10] and other components in these fruits have been reported. In order to search for biologically active principles from this drug, further studies have been undertaken.

RESULTS AND DISCUSSION

Nine components (**1–9**) were isolated from the MeOH extract of the dried fruits of *E. rutaecarpa*. All these components gave red–brown spots with Dragendorff's reagent on TLC. The structures of components **1–6** were identified as 1-methyl-2-nonyl-4(1H)-quinolone(**1**), 1-methyl-2-undecyl-4(1H)-quinolone(**2**), 1-methyl-2-dodecyl-4(1H)-quinolone(**3**), 2-tridecyl-4(1H)-quinolone(**4**), dihydroevocarpine(**5**), 1-methyl-2-pentadecyl-4(1H)-quinolone(**6**). The other three components (**7–9**) each showed a single peak on HPLC and further separation of each component using normal and reverse-phase HPLC columns under various solvent systems was unsuccessful. However, spectral data and chemical transformations indicated that each of them was a mixture of two isomers differing in the position of the double bond. Their structures were elucidated as 1-methyl-2-[(*Z*)-5-undecenyl]-4(1*H*)-quinolone (**7a**) and 1-methyl-2-[(*Z*)-6-undecenyl]-4(1*H*)-quinolone



	R^1	R^2
1	Me	
2	Me	
3	Me	
4	H	
5	Me	
6	Me	
7a	Me	5' 6'
7b	Me	6' 7'
8a	Me	7' 8'
8b	Me	8' 9'
9a	Me	9' 10'
9b	Me	10' 11'

Fig. 1. The structures of the quinolone alkaloids.

(**7b**) for **7**, 1-methyl-2-[(*Z*)-7-tridecenyl]-4(1*H*)-quinolone (**8a**) and evocarpine (**8b**) for **8**, and 1-methyl-2-[(*Z*)-9-pentadecenyl]-4(1*H*)-quinolone (**9a**) and 1-methyl-2-[(*Z*)-10-pentadecenyl]-4(1*H*)-quinolone (**9b**) for **9**. Compounds **3**, **4**, **7a**, **8a** and **9a** have not been reported before. The other seven compounds are known quinolone alkaloids.

Compound **3** was present in very small amount. Its UV and IR spectra showed the characteristic absorptions of 4(1*H*)-quinolone compounds [10, 11]. The EI-mass spectrum indicated the $[M]^+$ at *m/z* 327 and the characteristic fragment ions of *N*-methyl-4(1*H*)-quinolone alkaloids at *m/z* 186, 173 (base peak) and 144. A set of fragment ions with a 14 amu difference suggested the presence of an aliphatic side-chain. Deduction of *m/z* 158, the mass of the *N*-methyl-4(1H)-quinolone nuclei, from the $[M]^+$ (*m/z* 327) gave the mass of the side-chain, $C_{12}H_{25}$. Both the ^1H and ^{13}C NMR spectra exhibited signals due to the quinolone skeleton with an aliphatic chain of twelve carbon atoms [11] (Table 1). The structure of **3** was thus elucidated as 1-methyl-2-dodecyl-4(1*H*)-quinolone.

Compound **4** was obtained as an amorphous powder. The λ_{max} of the UV spectrum at 212, 235, 314 and 326 nm were shifted by *ca* 7 nm compared with that of compound **3**, indicating that the N in the ring of **4** was unsubstituted [12]. The EI-mass spectrum with $[M]^+$ at *m/z* 327, base peak at *m/z* 159 and other characteristic peaks relating to the ring at *m/z* 172 and 130, supported the existence of an *N*-demethyl quinolone skeleton. A set of fragment ions with a 14 amu difference led to the proposal of the presence of an aliphatic side-chain of $C_{13}H_{27}$. A weak carbonyl band at 1636 cm^{-1} in the IR spectrum, the absence of a carbonyl carbon atom, the shift of signals of C-3, C-4a and C-5 by *ca* 2–3 p.p.m. to high field and C-8 to lower field in ^{13}C NMR spectrum, can be explained by the carbonyl group being present in the enol form. The ^1H NMR spectrum showed signals due to a quinolone skeleton and the conjugated olefinic proton, δ 6.52 (1H, *s*, 3-H), was *ca* 0.15 p.p.m. lower than that of **3** due to aromatization of the heterocyclic ring by enolization. Therefore, **4** was assigned as 2-tridecyl-4-(1*H*)-quinolone, in which the carbonyl group may be completely or partially enolized to give 2-tridecyl-4-hydroxy-quinoline, depending on the medium [13].

Component **7** was an oil. Its UV absorption and IR spectra were similar to those of 1-methyl-2-[(*Z*)-6-undecenyl]-4(1*H*)-quinolone [11]. The EI-mass spectrum showed a $[M]^+$ at *m/z* 311 and characteristic fragmentations at *m/z* 186 (base peak), 173 and 144, which resembled those of **3**, suggesting the presence of an *N*-methyl quinolone skeleton with an alkenyl chain of $C_{11}H_{21}$ $[M-158]^+$. Two sets of fragments observed at *m/z* 268, 214 and 254, 200 in the mass spectrum might have originated from allylic cleavage of the two double bonds. With a $\Delta^{6'}$ side-chain cleavage between C-8′ and C-9′, and between C-4′ and C-5′,

Table 1. ^{13}C NMR (125 MHz) chemical shifts of quinolone alkaloids

	3*	**4***	**5***	**7a (b)***	**8a (b)†**	**9a (b)***
2	155.4	156.9	154.5	154.6	158.8	155.5
3	110.9	107.1	111.1	111.1	111.1	110.9
4	177.2	—	177.8	177.7	179.6	177.0
4a	126.1	124.6	126.5	126.5	127.0	126.0
5	126.6	124.9	126.6	126.7	126.7	126.6
6	123.6	123.5	123.4	123.3	125.1	123.7
7	132.2	132.4	132.1	132.0	133.8	132.3
8	115.4	119.0	115.3	115.3	117.8	115.4
8a	141.9	140.3	142.0	142.0	143.5	142.0
N-Me	34.0	—	34.1	34.1	35.4	34.4
1′	34.8	34.3	34.8	34.7	35.6	34.9
2′	28.6	28.2	28.6	38.5	29.6[f]	28.6[i]
3′	29.3[a]	29.3[b]	29.3[c]	29.4[d]	30.2[f]	29.0[i]
4′	29.3[a]	39.3[b]	29.5[c]	26.9 (28.9)	30.2[f]	29.4[i]
5′	29.4[a]	29.5[b]	29.5[c]	129.1[e] (26.9)	30.8[f]	29.3[i]
6′	29.4[a]	29.5[b]	29.6[c]	130.4[e] (129.1)	28.1[g] (29.7)	29.4[j]
7′	29.4[a]	29.6[b]	29.6[c]	26.9 (130.4)	130.7[h] (28.1)	29.7[j]
8′	29.6[a]	29.8[b]	29.6[c]	28.9[d] (26.9)	130.9[h] (130.7)	26.9[j] (29.2)
9′	29.6[a]	29.8[b]	29.6[c]	31.9	27.9[g] (130.9)	129.9[k] (26.9)
10′	31.9	29.8[b]	29.6[c]	22.9	29.7[f] (27.9)	130.1[k] (129.6)
11′	22.6	31.9	31.9	14.0	33.1	27.2[j] (130.8)
12′	14.0	22.7	22.6	—	23.3	29.2[j] (27.2)
13′	—	14.1	14.1	—	14.3	32.0
14′	—	—	—	—	—	22.3
15±1	—	—	—	—	—	14.0

[a–k]Assignments may be interchanged in each column.

*In $CDCl_3$.

†In CD_3OD.

accounted for *m/z* 268 $[M-C_3H_7]^+$ and 214 $[M-C_7H_{13}]^+$, correspondingly. Similarly, the fragments of *m/z* 254 and 200 came from the $\Delta^{5'}$ side-chain. In the ^{1}H NMR spectrum, besides the signals expected for the *N*-methyl quinolone skeleton, a double bond multiplet at δ 5.35 was observed. Both double bonds were suggested to be in the *Z*-form based on the ^{13}C NMR chemical shift of the allyl carbons (δ 26.9) [11, 14]. On catalytic hydrogenation, **7** was converted to **2**. When **7** was oxidized with OsO_4–$NaIO_4$ followed by treatment with 2,4-dinitrophenylhydrazine, the reaction mixture gave two peaks (*Rt* 5.49 and 5.90 min) on HPLC with a ratio of 3:1. The R_fs were identical to those of the 2,4-dinitrophenylhydrazones of hexanal and pentanal, respectively. The results of the chemical transformations confirmed that **7** was a mixture of 1-methyl-2-[(*Z*)-5-undecenyl]-4(1H)-quinolone (**7a**) and 1-methyl-2[(*Z*)-6-undecenyl]-4(1H)-quinolone (**7b**).

Components **8** and **9** were also oils. Their UV, IR and ^{1}H NMR spectra resembled those of **7**, exhibiting signals due to the quinolone skeleton [11, 15]. The EI-mass spectra of **8** and **9** showed a $[M]^+$ at *m/z* 339 and 367, respectively, and both of them exhibited the characteristic fragment ions of quinolone alkaloids at *m/z* 186, 173 and 144. Two sets of fragments of *m/z* 282, 228 and *m/z* 296, 242 were observed in the mass spectrum of **8** and also two sets of *m/z* 310, 256 and *m/z* 324, 270 in that of **9**. The ^{13}C NMR chemical shifts of the allyl carbon of **8** were δ 27.9 and 28.1, while that of **9** were at δ 27.0 and 27.2. On catalytic hydrogenation, **8** was converted to **5** and **9** was converted to **6**. By treatment with OsO_4–$NaIO_4$ and 2,4-dinitrophenylhydrazine, both the reaction mixtures of **8** and **9** showed two peaks (R_f 5.49 and 5.90 min) on HPLC in the ratio of 10:1 (**8**) and 1.2:1 (**9**), corresponding to the 2,4-dinitrophenylhydrazones of pentanal and hexanal, respectively. By analyses of the spectral data and chemical transformations analogous to that of **7**, it can be concluded that both **8** and **9** were mixtures of two isomers differing in the positions of the double bond. Compound **8** was a mixture of 1-methyl-2-[(*Z*)-7-tridecenyl]-4(1H)-quinolone (**8a**) and evocarpine (**8b**), and **9** was a mixture of 1-methyl-2-[(*Z*)-9-pentadecenyl]-4(1*H*)-quinolone (**9a**) and 1-methyl-2-[(*Z*)-10-pentadecenyl]-4(1*H*)-quinolone(**9b**).

EXPERIMENTAL

General. Mps: uncorr. ^{1}H and ^{13}C NMR were recorded at 500 MHz and 125 MHz, respectively, with TMS as int. standard.

Plant material. Fruits of *Evodia rutaecarpa* Bentham were collected in Sichuan Provence in 1990 and identified by Prof. Min-ru Jia (Sichuan Traditional Chinese Medical College). A voucher specimen is kept in the Dept of Plant Science, Institute of Materia Medica, Chinese Academy of Medical Sciences.

Extraction and isolation. Dried fruits were extracted ×3 with petrol, then ×3 with MeOH under reflux. The concd MeOH extract was separated by silica gel CC (petrol–EtOAc) to give a quinolone alkaloid mixt. This was subjected to chromatography on a $AgNO_3$–silica gel (1:19) column (petrol–EtOAc–MeOH, 4:2:1) to give different frs. Each fr. was further separated by MPLC (column: RP C8, MeOH–H_2O–HOAc, (8:2:0.1), then purified by prep. TLC on $AgNO_3$–silica gel (1:19) and then desalted using prep. TLC on silica gel GF_{254} to give compounds **1–6** and component **7–9**.

1-*Methyl*-2-*dodecyl*-4(1H)-*quinolone* (**3**). Crystals, mp. 75–76°. UV λ_{max}^{EtOH} nm (log ε): 212 (4.44), 238 (4.48), 321 (4.16), 333 (4.17). IR ν_{max}^{KBr} cm^{-1}: 2916, 2852, 1635, 1597, 1572, 1471, 1417, 1301, 1188, 830, 777, 760. EIMS 70 eV, *m/z* (rel, int): 327 $[M]^+$, (15), 312 (5), 298 (15), 284 (14), 270 (12), 256 (8), 242 (5), 228 (5), 214 (2), 200 (10), 186 (80), 173 (100), 144 (20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (1H, *dd*, *J* = 1.5, 8.0 Hz, H-5), 7.68 (1H, *dt*, *J* = 1.5, 8.0 Hz, H-7), 7.53 (1H, *d*, *J* = 8.0 Hz, H-8), 7.38 (1H, *t*, *J* = 8.0 Hz, H-6). 6.37 (1H, *s*, H-3), 3.77 (3H, *s*, *N*-Me), 2.73 (2H, *t*, *J* = 7.8 Hz, H-1′), 1.68 (2H, *m*, H-2′), 1.42 (2H, *m*, H-3′), 1.25–1.35 (16H, *m*), 0.87 (3H, *t*, *J* = 7.1 Hz, H-12′). ^{13}C NMR: Table 1.

2-*Tridecyl*-4(1H)-*quinolone* (**4**). Amorphous powder, mp 132–134°. UV λ_{max}^{EtOH} nm (log ε): 212 (4.49), 235 (4.48), 314 (4.13), 326 (4.12). IR ν_{max}^{KBr} cm^{-1}: 3060, 2950, 2920, 2849, 1636, 1593, 1553, 1503, 1472, 1440, 1350, 1160, 820, 770, 759. EIMS 70 eV, *m/z* (rel, int): 327 ($[M]^+$, 18), 312 (5), 298 (12), 284 (14), 270 (12), 256 (8), 242 (5), 228 (10), 214 (8), 200 (2), 186 (20), 172 (80), 159 (100), 130 (18). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (1H, *dd*, *J* = 1.5, 8.0 Hz, H-5), 8.06 (1H, *d*, *J* = 8.0 Hz, H-8), 7.65 (1H, *dt*, *J* = 1.5, 8.0 Hz, H-7), 7.42 (1H, *t*, *J* = 8.0 Hz, H-6), 6.52 (1H, *s*, H-3), 2.85 (2H, *t*, *J* = 8.0 Hz, H-1′), 1.76 (2H, *m*, H-2′), 1.24 (20H, *m*), 0.85 (3H, *t*, *J* = 7.6 Hz, H-13′). ^{13}C NMR: Table 1.

1-*Methyl*-2-[(Z)-5-*undecenyl*]-4-(1H)-*quinolone* (**7a**) *and* 1-*methyl*-2-[(Z)-6-*undecenyl*]-4-(1H)-*quinolone* (**7b**). UV λ_{max}^{MeOH} nm (log ε): 213 (4.36), 238 (4.41), 320 (4.08), 332 (4.10). IR ν_{max}^{KBr} cm^{-1}: 2960, 2928, 2856, 1626, 1599, 1499, 1468, 1180, 760. EIMS 70 eV, *m/z* (rel, int): 311 ($[M]^+$, 25), 296 (4), 282 (40), 268 (10), 254 (8), 240 (2), 228 (12), 214 (4), 200 (15), 186 (100), 173 (70), 144 (10). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.44 (1H, *dd*, *J* = 1.5, 8.0 Hz, H-5), 7.65 (1H, *dt*, *J* = 1.5, 8.0 Hz, H-7), 7.50 (1H, *d*, *J* = 8.0 Hz, H-8), 7.36 (1H, *t*, *J* = 8.0 Hz, H-6), 6.24 (1H, *s*, H-3), 5.35 (2H, *m*, olefinic proton), 3.73 (3H, *s*, *N*-Me), 2.70 (2H, *t*, *J* = 7.2, H-1′), 2.03 (4H, *m*, allyl proton), 1.68 (2H, *m*, H-2′), 1.26–1.47 (8H, *m*), 0.89 (3H, *m*, H-13′). ^{13}C NMR: Table 1.

1-*Methyl*-2-[(*Z*)-7-*tridecenyl*]-4-(1H)-*quinolone* (**7a**) *and evocarpine* (**7b**). UV λ_{max}^{MeOH} nm (log ε): 214 (4.44), 238 (4.50), 321 (4.16), 333 (4.18). IR ν_{max}^{KBr} cm^{-1}: 2950, 2926, 2853, 1637, 1596, 1572, 1496, 1464, 1175, 777. EIMS 70 eV, *m/z* (rel, int): 339 ($[M]^+$, 30), 324 (2), 310 (50), 296 (20), 282 (5), 256 (7), 242 (12), 228 (8), 214 (2), 200 (20), 186 (100), 173 (80), 144 (20).

^{1}H NMR (500 MHz, CD_3OD): δ 8.35 (1H, *dd*, $J = 1.5$, 8.0 Hz, H-5), 7.87 (1H, *dd*, $J = 1.2$, 8.0 Hz, H-8), 7.82 (1H, *m*, H-7), 7.50 (1H, *dt*, $J = 1.2$, 8.0 Hz, H-6), 6.34 (1H, *s*, H-3), 5.37 (2H, *m*, olefinic proton), 3.92 (3H, *s*, *N*-Me), 2.91 (2H, *t*, $J = 7.2$ Hz, H-1′), 2.07 (4H, *m*, allyl proton), 1.77 (2H, *m*, H-2′), 1.29–1.53 (12H, *m*), 0.93 (3H, *t*, $J = 7.0$ Hz, H-13′). ^{13}C NMR: Table 1.

1-*Methyl*-2-[(Z)-9-*pentadecenyl*]-4(1H)-*quinolone* (**9a**) *and* 1-*methyl*-2 [(*Z*-10-*pentadecenyl*]-4(1H)-*quinolone* (**9b**). UV λ_{max}^{MeOH} nm (log ε): 214 (4.46), 239 (4.51), 320 (4.18), 333 (4.20). IR ν_{max}^{KBr} cm^{-1}: 2950, 2926, 2853, 1627, 1599, 1565, 1500, 1469, 1180, 759. EIMS 70 eV, *m/z* (rel, int): 367 ([M]$^+$, 18), 352 (4), 338 (50), 324 (40), 310 (15), 296 (5), 284 (5), 282 (6), 270 (16), 256 (10), 242 (10), 228 (12), 214 (2), 200 (20), 186 (100), 173 (96), 144 (20). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (1H, *dd*, $J = 1.5$ Hz, 8.0 Hz, H-5), 7.70 (1H, *m*, H-7), 7.55 (1H, *d*, $J = 8.0$ Hz, H-8), 7.40 (1H, *t*, $J = 8.0$ Hz, H-6), 6.42 (1H, *s*, H-3), 5.34 (2H, *m*, olefinic proton), 3.79 (3H, *s*, *N*-Me), 2.75 (2H, *t*, $J = 7.6$ Hz, H-1′), 2.01 (4H, *m*, allyl proton), 1.68 (2H, *m*, H-2′), 1.25–1.47 (16H, *m*), 0.88 (3H, $J =$ 7.0 Hz, H-15′). ^{13}C NMR: Table 1.

Catalytic hydrogenation. A soln of the alkaloid (*ca* 2 mg) in EtOH (2 ml) with 5% Pd–C (3 mg) as catalyst was stirred for 3 hr under H_2 and the catalyst then filtered off. The soln was concd. The R_f value on TLC (petrol–EtOAc–MeOH, 10:5:1) and the R_t on HPLC (Lichrosorb RP C8, MeOH–H_2O, 17:3) UV 321 nm) of the product was checked with that of corresponding known compounds [11].

Lemieux–Johnson oxidation. OsO_4 (2 mg) and $NaIO_4$ (20 mg) in H_2O (2 ml) were added to a soln of the alkaloid (2 mg) to be tested in 1 ml of H_2O–THF (1:4). The mixt. was stirred for 24 hr and extracted with Et_2O. The Et_2O layer, after being dried (Na_2SO_4), was treated with an Et_2O soln of 2,4-dinitrophenylhydrazine in the presence of catalytic amount of concd HCl. After washing the reaction mixt. with H_2O, the Et_2O was evapd off. The residue was dissolved in MeOH and analysed by HPLC (Lichrosorb RP C8, MeOH–H_2O, 17:3, UV 360 nm). Two peaks (R_t 5.49 and 5.90 min) of the spectrum were identical with that of the standard hydrazones of pentanal and hexanal [11, 16].

Acknowledgement—This research was supported by a grant from the Chinese National Natural Science Foundation.

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