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Studies on the Chemical Constituents of Rutaceous Plants. XLVI.[1] The Chemical Constituents of *Xanthoxylum integrifoliolum* (Merr.) Merr. (*Fagara integrifoliola* Merr.) II.[2] Structural Establishment of Integriquinolone, a New Phenolic Quinolone

Hisashi Ishii,*,[a] Kazuo Koyama,[a] Ih-Sheng Chen,[b] Sheng-Teh Lu,[b] and Tsutomu Ishikawa[a]

Faculty of Pharmaceutical Sciences, Chiba University,[a] 1-33, Yayoi-cho, Chiba, 260, Japan and School of Pharmacy, Kaohsiung Medical College,[b] No. 100, Shih-chuan 1st. Road, Kaohsiung, Taiwan

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The structure of integriquinolone (1), a new phenolic quinolone which was isolated from *Xanthoxylum integrifoliolum* (Merr.) Merr. (*Fagara integrifoliola* Merr.), was established as 6-hydroxy-4-methoxy-1-methyl-2-quinolone by synthesis of ethyl integriquinolone (2), 6-ethoxy-4-methoxy-1-methyl-2-quinolone.

Keywords——structural establishment; Rutaceae; *Xanthoxylum* species; 2-quinolone; integriquinolone

In the course of studies on the chemical constituents of Rutaceous plants, we[2] have isolated a new phenolic 2-quinolone (**1**) from the root wood of *Xanthoxylum integrifoliolum* (Merr.) Merr. (*Fagara integrifoliola* Merr.), a Formosan plant, in 0.00045% yield and designated it as integriquinolone. In this report, we give full details of the structural establishment of this new phenolic quinolone (**1**) by synthesis of its *O*-ethyl derivative, ethyl integriquinolone (**2**).

Integriquinolone (**1**) was obtained as colorless needles, mp 257—260°C [$C_{11}H_{11}NO_3$ (M^+: at m/z 205)]. In the infrared (IR) spectrum, it shows a hydroxy or an NH band at 3150 cm^{-1} and a carbonyl band at 1640 cm^{-1}. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, it exhibits two sharp 3H singlets attributable to a methoxyl group or an amide methyl group at 4.14 and 4.26 δ. In the aromatic region, two doublets appear at 7.90 δ (J=

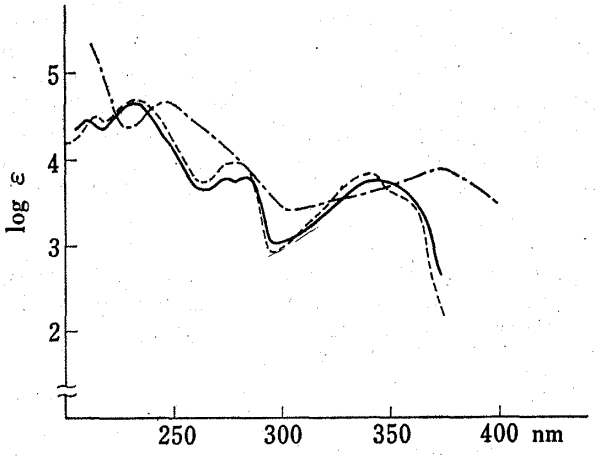
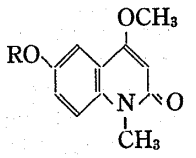


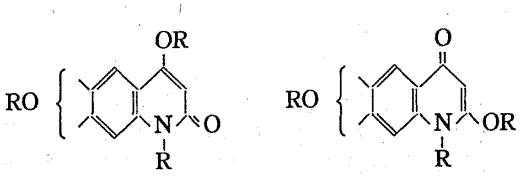
Fig. 1. UV Spectra of Integriquinolone (**1**) and Ethyl Integriquinolone (**2**)

——: **1** in EtOH.
——: **1** in EtOH/NaOH.
----: **2** in EtOH.



1: R=H
2: R=CH_2CH_3

Chart 1



3 **4**

Chart 2

3.0 Hz) and at 7.93 δ (J=10.0 Hz) and a double doublet at 7.09 δ (J=10.0 and 3.0 Hz), indicating that integriquinolone (**1**) has a 1,2,4-trisubstituted benzene ring in its molecule. In addition, one 1H singlet is observed at 6.81 δ. The ultraviolet (UV) spectrum of integriquinolone (**1**) shows maxima at 231 (4.64), 272 (3.84), 282 (3.80), and 343 (3.78) nm (log ε) and a bathochromic shift upon addition of 4% NaOH aq. (Fig. 1). Chemically, integriquinolone (**1**) gave ethyl integriquinolone (**2**) on treatment with diazoethane. In the IR spectrum, it shows no hydroxy or NH band but a carbonyl band at 1663 cm^{-1}. In view of the natural occurrence of 2,4-dioxygenated quinoline alkaloids[3] in Rutaceous plants, integriquinolone (**1**) might be a 4-oxygenated 2-quinolone (**3**) or a 2-oxygenated 4-quinolone (**4**) having an oxygen function at its C_6 or C_7 position.

There are many reports on the discrimination between a 4-hydroxy-2-quinolone and a 2-hydroxy-4-quinolone derivative on the basis of the IR,[4,5] UV,[4,6] and ^{1}H-NMR[7] spectra. However, since the spectral data of these quinolone derivatives fall in a relatively wide range, we could not rigidly establish the structure in this way. Therefore, we undertook to establish the structure of integriquinolone (**1**) by synthesis of ethyl integriquinolone (**2**). We began our project with synthesis of 6-ethoxy-4-hydroxy-1-methyl-2-quinolone (**5**) since the condensation of *N*-methyl-*p*-phenetidine (**6**) with malonic acid provides the required 6-ethoxyquinolone (**5**) as a single product, while that of *N*-methyl-*m*-phenetidine (**7**) with malonic acid provides a mixture of 5- (**8**) and 7- (**9**) ethoxyquinolone.[8]

N-Methyl-*p*-phenetidine (**6**) was prepared *via* benzyloxycarbonylation of *p*-phenetidine followed by *N*-methylation with silver oxide and methyl iodide in dimethylformamide (DMF) and by hydrolysis with conc. hydrochloric acid in methanol in 79% total yield. A mixture of *N*-methyl-*p*-phenetidine (**6**) and malonic acid was treated with phosphorus oxychloride to give the desired 6-ethoxy-4-hydroxy-1-methyl-2-quinolone (**5**) in 31% yield.

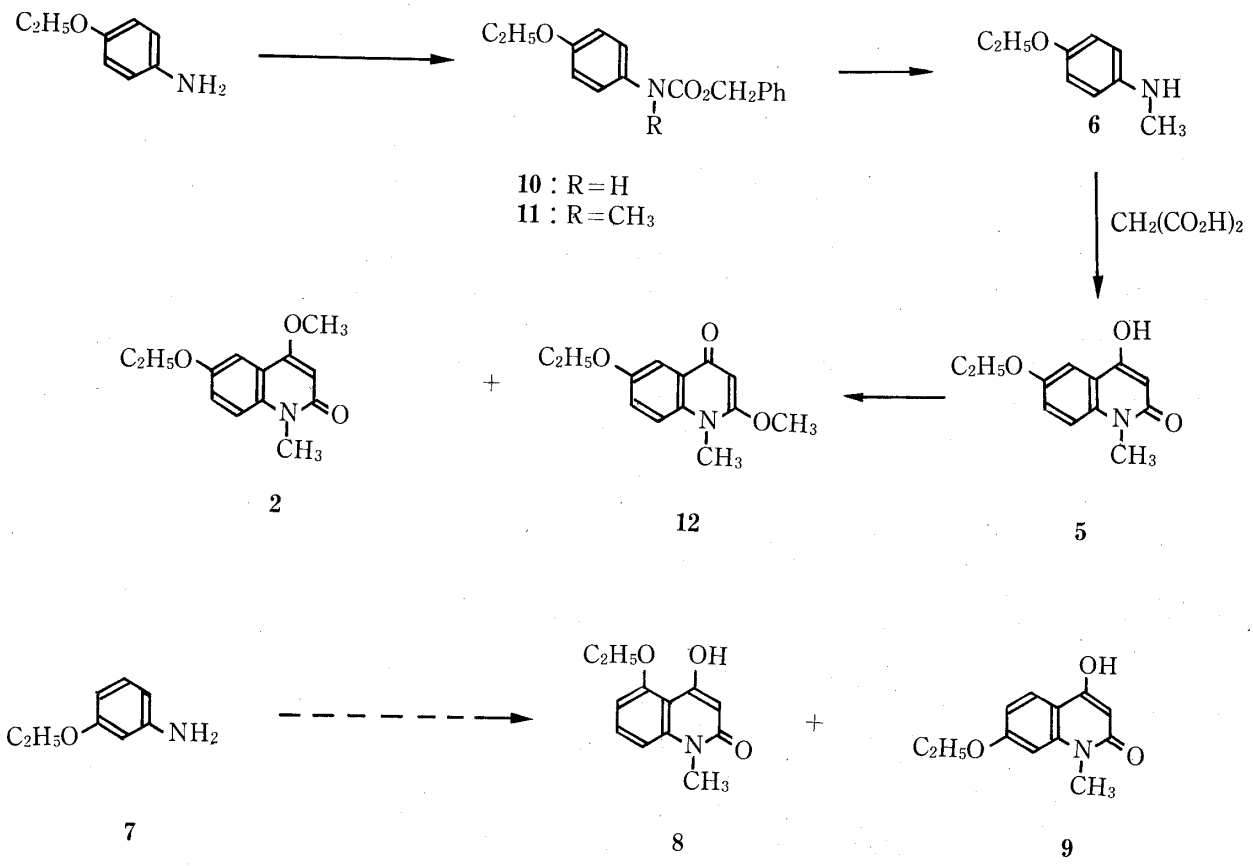


Chart 3

Treatment of 6-ethoxy-4-hydroxy-1-methyl-2-quinolone (**5**) with diazomethane gave a mixture of two quinolone products (**2** and **12**) in 81 and 13% yields, respectively. The major product (**2**) was identical with ethyl integriquinolone. It is well known that methylation of a 4-hydroxy-1-methyl-2-quinolone derivative gives the 4-methoxy-1-methyl-2-quinolone derivative as a major product along with the 2-methoxy-1-methyl-4-quinolone as a by-product. Although this consideration allows us to suppose that ethyl integriquinolone (**2**) is 6-ethoxy-2-methoxy-1-methyl-4-quinolone, it does not represent unequivocal proof. We therefore carried out chemical transformation as follows.

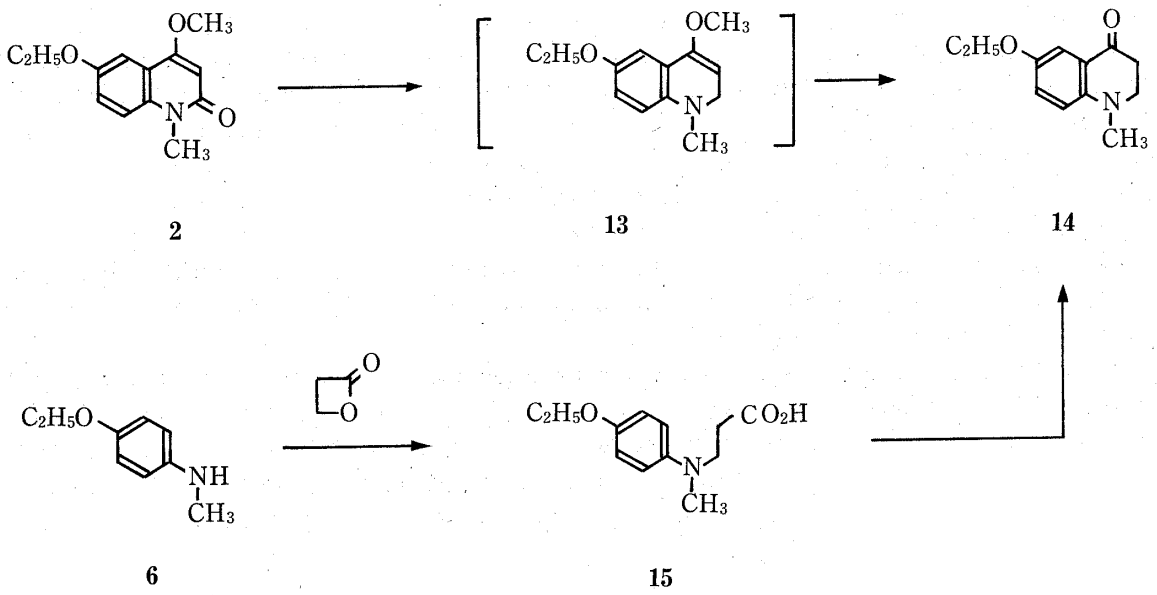


Chart 4

Reduction of the synthetic ethyl integriquinolone (**2**) with lithium aluminium hydride followed by treatment with oxalic acid gave a dihydroquinolone derivative as an oily product which was characterized as the phenylhydrazone, $C_{18}H_{21}N_3O$, mp 113—115°C. On the other hand, treatment of *N*-methyl-*p*-phenetidine (**6**) with propiolactone gave 3-(*N*-methyl-*p*-phenetidino)propionic acid (**15**) which provided 2,3-dihydro-6-ethoxy-1-methyl-4-quinolone (**14**) on treatment with phosphorus pentoxide in xylene. The former dihydroquinolone phenylhydrazone gave an IR spectrum identical with that of an authentic sample of the latter 4-quinolone derivative. These results allow us unequivocally to assign integriquinolone as 6-hydroxy-4-methoxy-1-methyl-2-quinolone (**1**).

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. IR and UV spectra were recorded on a Hitachi 295 spectrometer in Nujol and on a Hitachi 340 spectrophotometer for solutions in 95% ethanol, respectively. ^{1}H-NMR spectra were recorded on a JEOL JNM-4H-100 spectrometer in deuteriochloroform, with tetramethylsilane as an internal reference. All NH and OH signals were confirmed by disappearance of their signals after addition of deuterium oxide. Mass spectra (MS) were measured on a Hitachi RMU-6E spectrometer at 70 eV chamber voltage with a direct inlet system. For chromatography (by column), Silica Gel 60 (70—230 mesh ASTM), Merck, and for preparative thin layer chromatography (TLC), Silica Gel GF_{254}, Merck, were used. All identification of products was done by IR and TLC comparisons, and mixed melting point determination. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; br, broad; sh, shoulder.

Integriquinolone (1)——As reported in the previous paper,[2] integriquinolone (**1**) was isolated in 0.00045% yield from the root wood of *X. integrifoliolum* (Merr.) Merr. (*F. integrifoliola* Merr.) along with ten alkaloids [dictamnine, skimmianine, 4-methoxy-1-methyl-2-quinolone, arnottianamide, α-allocryptopine, robustine, haplopine, (+)-platydesmine, myrtopsine, and integriamide], five coumarins [5,6,7-trimethoxycoumarin,

6,7,8-trimethoxycoumarin, aesculetin dimethyl ether, fraxinol, and unknown coumarin I], and five other components [lupeol, β-sitosterol, *d*-sesamin, 2,6-dimethoxy-*p*-benzoquinone, and *dl*-syringaresinol]. Recrystallization of crude integriquinolone (**1**) from MeOH gave colorless needles, mp 257—260°C. *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.33; H, 5.37; N, 6.78. IR ν_{max}^{KBr} cm^{-1}: 3150 (OH), 1640 (CO). ^{1}H-NMR (CF_3COOH) δ: 4.14 and 4.26 (each 3H, s, NCH_3 and OCH_3), 6.81 (1H, s, arom. H), 7.09 (1H, dd, J=10.0 and 3.0 Hz, arom. H), 7.90 (1H, d, J=3.0 Hz, arom. H), 7.93 (1H, d, J=10.0 Hz, arom. H). MS *m/z*: 205 (M^+, 100%). UV λ_{max}^{KBr} nm (log ε): 231 (4.64), 272 (3.84), 282 (3.80), 343 (3.78).

Ethyl Integriquinolone (2)——A solution of a large excess of diazoethane in ether was added to a solution of integriquinolone (**1**) (0.022 g) in MeOH (15 ml). The mixture was kept at room temperature for 1 week and evaporated to dryness *in vacuo*. Recrystallization of the residue from MeOH gave colorless needles (0.013 g), mp 168—169°C. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.71; H, 6.46; N, 5.99. IR ν_{max} cm^{-1}: 1663 (CO). ^{1}H-NMR δ: 1.43 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.64 and 3.94 (each 3H, s, NCH_3 and OCH_3), 4.09 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.02 (1H, s, arom. H), 7.16—7.35 (2H, m, arom. H), 7.38 (1H, d, J=3.0 Hz, arom. H). MS *m/z*: 233 (M^+, 100%). UV λ_{max}^{EKr} nm (log ε): 215 (4.47), 233 (4.69), 273 (3.80), 282 (3.77), 341 (3.79), 355 (3.68) sh.

***N*-Benzyloxycarbonyl-*p*-phenetidine (10)**——Benzyl chloroformate (carbobenzoxy chloride) (57.61 g) was added dropwise to a stirred suspension of *p*-phenetidine (30.00 g) in 10% NaOH aq. (150 ml) at room temperature. After the mixture had been stirred for 1 h, the precipitate was collected by filtration and recrystallized from EtOH–H_2O to give colorless leaflets (52.23 g), mp 109—110°C. *Anal.* Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.96; H, 6.28; N, 5.19. IR ν_{max}^{KBr} cm^{-1}: 3330 (NH), 1700 (CO). ^{1}H-NMR δ: 1.36 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.97 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.13 (2H, s, OCH_2Ph), 6.57 (1H, br s, NH), 6.78 (2H, d, J=9.0 Hz, C_2- and C_6-H), 7.22 (2H, d, J=9.0 Hz, C_3- and C_5-H), 7.33 (5H, s, Ph).

***N*-Benzyloxycarbonyl-*N*-methyl-*p*-phenethidine (11)**——A mixture of *N*-benzyloxycarbonyl-*p*-phenetidine (**10**) (10.01 g), methyl iodide (18.5 ml), and Ag_2O (34.53 g) in DMF (150 ml) was stirred at room temperature for 3 h. Excess Ag_2O was filtered off and washed with DMF (*ca.* 50 ml). The filtrate and washings were combined and concentrated by distilling off the solvent under reduced pressure, The precipitate (AgI) was removed by filtration and washed again with ether. The filtrate and ethereal washings were combined. A large amount of water was added, then the solution was extracted with ether. The ethereal solution was washed with 5% KCN aq. (*ca.* 100 ml) and then with water, dried over $MgSO_4$, and evaporated to dryness to give pale yellow prisms (10.40 g), mp 46—49°C. Recrystallization of a part of the crude material from hexane gave an analytical sample, colorless prisms, mp 49—50°C. *Anal.* Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.49; H, 6.72; N, 4.78. IR ν_{max}^{KBr} cm^{-1}: 1700 (CO). ^{1}H-NMR δ: 1.38 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.24 (3H, s, NCH_3), 3.99 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.11 (2H, s, OCH_2Ph), 6.81 (2H, d, J=9.0 Hz, C_2- and C_6-H), 7.10 (2H, d, J=9.0 Hz, C_3- and C_5-H), 7.26 (5H, s, Ph).

The crude material was used for the subsequent step without purification.

***N*-Methyl-*p*-phenetidine (6)**——A solution of *N*-benzyloxycarbonyl-*N*-methyl-*p*-phenetidine (**11**) (9.19 g) in MeOH (70 ml) and conc. HCl (90 ml) was refluxed for 3 h and evaporated to dryness *in vacuo*. The residue was dissolved in water, basified with 10% NaOH aq., and extracted with ether. The ethereal solution was dried over K_2CO_3 and evaporated to dryness. Distillation of the oily residue at 125—130°C (15 mmHg) [lit.[9] bp 164°C (40 mmHg)] gave a pale yellow oil (4.43 g). IR ν_{max}^{neat} cm^{-1}: 3430 (NH). ^{1}H-NMR δ: 1.35 (3H, t, J=6.5 Hz, $CH_2C\underline{H}_3$), 2.78 (3H, s, NCH_3), 3.34 (1H, s, NH), 3.95 (2H, q, J=6.5 Hz, $OC\underline{H}_2CH_3$), 6.52 (2H, d, J=9.0 Hz, C_3- and C_5-H), 6.72 (2H, d, J=9.0 Hz, C_2- and C_6-H).

6-Ethoxy-4-hydroxy-1-methyl-2-quinolone (5)——A mixture of *N*-methyl-*p*-phenetidine (**6**) (1.001 g), malonic acid (1.287 g), and $POCl_3$ (1.92 ml) was heated at 95°C for 20 min in an open flask. The mixture was poured into ice-water and basified (pH 10) with 10% NaOH aq. The solution was washed with AcOEt. The aqueous layer was acidified (pH 2) with 10% HCl aq. and the resultant precipitate was collected by filtration (1.135 g). Purification of the precipitate by column chromatography on SiO_2 with a mixed solvent [$CHCl_3$: AcOEt=1: 1 (v/v)] gave colorless prisms (0.410 g), mp 291—294°C, which were recrystallized from EtOH. *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.91; N, 6.39. Found: C, 65.81; H, 5.98; N, 6.39. IR ν_{max}^{KBr} cm^{-1}: 1620, 1590, 1550. ^{1}H-NMR (DMSO-d_6) δ: 2.33 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.49 (3H, s, NCH_3), 4.06 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 5.85 (1H, s, C_3–H), 7.17 (1H, dd, J=9.0 and 3.0 Hz, C_7–H), 7.30 (1H, d, J=3.0 Hz, C_5–H), 7.36 (1H, d, J=9.0 Hz, C_8–H).

Synthetic Ethyl Integriquinolone (2) (6-Ethoxy-4-methoxy-1-methyl-2-quinolone)——i) 6-Ethoxy-4-methoxy-1-methyl-2-quinolone (**2**): A solution of an excess of CH_2N_2 in ether was added to a solution of 6-ethoxy-4-hydroxy-1-methyl-2-quinolone (**5**) (0.508 g) in MeOH (200 ml). The mixture was left to stand at room temperature overnight and then evaporated to dryness *in vacuo*. The residue (0.560 g) was chromatographed on SiO_2 with a mixed solvent [AcOEt: $CHCl_3$=2: 1 (v/v)]. The first eluate gave colorless needles (0.438 g), mp 165—167°C which were recrystallized from MeOH–Et_2O. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.74; H, 6.43; N, 5.96. IR ν_{max}^{KBr} cm^{-1}: 1663 (CO). ^{1}H-NMR δ: 1.43 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.63 and 3.93 (each 3H, s, NCH_3 and OCH_3), 4.08 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.01 (1H, s, C_3–H), 7.15—7.33 (2H, m, C_7– and C_8–H), 7.36 (1H, d, J=3.0 Hz, C_5–H). MS *m/z*: 233 (M^+, 100%).

This material was identical with a sample of ethyl integriquinolone which was derived from the naturally occurring integriquinolone (**1**).

ii) 6-Ethoxy-2-methoxy-1-methyl-4-quinolone (**12**): The subsequent eluate gave colorless prisms (0.070 g), mp 145—146°C, which were recrystallized from EtOH–H_2O. *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.02; H, 6.48; N, 5.90. IR ν_{max}^{KBr} cm^{-1}: 1666, 1603, 1565, 1552. ^{1}H-NMR δ: 1.45 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.65 and 3.96 (each 3H, s, NCH_3 and OCH_3), 4.16 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 5.82 (1H, s, C_3–H), 7.20—7.42 (2H, m, C_7– and C_8–H), 7.79 (1H, d, J=3.0 Hz, C_5–H).

2,3-Dihydro-6-ethoxy-1-methyl-4-quinolone (**14**)——i) 1,2-Dihydro-6-ethoxy-4-methoxy-1-methylquinoline (**13**): A solution of 6-ethoxy-4-methoxy-1-methyl-2-quinolone (**2**) (0.101 g) in dry THF (8.0 ml) was added to a suspension of $LiAlH_4$ (0.170 g) in dry THF (5.0 ml) under ice cooling. The mixture was stirred at room temperature for 1.5 h. After excess reagent had decomposed by addition of wet ether under ice cooling, the mixture was treated with an aqueous solution of Rochelle salt and filtered. The filtrate was extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness *in vacuo* to give a pale yellow oil (0.082 g).

ii) 2,3-Dihydro-6-ethoxy-1-methyl-4-quinolone (**14**): A solution of the oily product (0.082 g) in 1 M $(COOH)_2$ aq. (1.75 ml) was stirred at room temperature for 1 h. The solution was made alkaline with 10% NaOH aq. and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness to give a yellow oil (0.072 g). IR ν_{max}^{neat} cm^{-1}: 1680 (CO).

Phenylhydrazone: A solution of the crude oil (0.070 g) described above and phenylhydrazine (0.04 ml) in EtOH (2.0 ml) containing one drop of AcOH was refluxed for 1 h, then cooled. The resulting yellow precipitate was collected by filtration (0.094 g). Recrystallization of the precipitate from EtOH–H_2O gave yellow fine needles (0.047 g), mp 113—115°C. *Anal.* Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.23; H, 7.24; N, 14.30. IR ν_{max} cm^{-1}: 1603. ^{1}H-NMR[10] δ: 1.40 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.67 (2H, t, J=7.5 Hz, C_3–H_2), 2.82 (3H, s, NCH_3), 3.12 (2H, t, J=7.5 Hz, C_2–H_2), 4.03 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.59 (1H, d, J=9.0 Hz, C_8–H), 6.70—6.95 (1H, br s, NH), 6.80 (1H, dd, J=9.0 and 3.0 Hz, C_7–H), 7.17 (5H, s, Ph), 7.70 (1H, d, J=3.0 Hz, C_5–H).

3-(*N*-Methyl-*p*-phenetidino)propionic Acid (**15**)——Propiolactone (2.60 ml) was gradually added to a solution of *N*-methyl-*p*-phenetidine (**6**) (5.04 g) in dry CH_3CN (20.0 ml) at 81—83°C during 20 min with stirring. After the addition, the mixture was heated for a further 2.5 h with stirring and then evaporated to dryness *in vacuo*. The oily residue[11] was dissolved in 1 N NaOH aq. (100 ml) and the solution was stirred at room temperature for 1.5 h. The reaction mixture was washed with ether. The pH was adjusted to pH 4—5 with conc. HCl and the aqueous layer was extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness to give a pale brown oil (5.406 g). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO). ^{1}H-NMR δ: 1.39 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.53 (2H, t, J=7.5 Hz, $CH_2C\underline{H}_2CO$), 2.85 (3H, s, NCH_3), 3.48 (2H, t, J=7.5 Hz, $NC\underline{H}_2CH_2$), 3.98 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.85 (4H, s, arom. H), 7.92 (1H, br s, COOH).

2,3-Dihydro-6-ethoxy-1-methyl-4-quinolone (**14**)——Phosphorus pentoxide (6.4 g) was added to a solution of 3-(*N*-methyl-*p*-phenetidino)propionic acid (**15**) (5.02 g) in dry xylene (60 ml) under a stream of nitrogen. The mixture was gently refluxed for 2 h and evaporated to dryness *in vacuo*. A large quantity of ice-water was added to the residue, then the mixture was basified with 10% NaOH aq., and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness. Column chromatography of the oily residue on SiO_2 with benzene gave a yellow oil (0.332 g). IR ν_{max}^{neat} cm^{-1}: 1680 (CO). ^{1}H-NMR δ: 1.38 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 2.20 (2H, t, J=7.5 Hz, C_3–H_2), 2.93 (3H, s, NCH_3), 3.39 (2H, t, J=7.5 Hz, C_2–H_2), 3.99 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.65 (1H, d, J=9.0 Hz, C_8–H), 7.04 (1H, dd, J=9.0 and 3.0 Hz, C_7–H), 7.36 (1H, d, J=3.0 Hz, C_5–H).

Phenylhydrazone: A solution of crude 2,3-dihydro-6-ethoxy-1-methyl-4-quinolone (**14**) (0.069 g) and phenylhydrazine (0.04 ml) in EtOH (2.0 ml) containing one drop of AcOH was refluxed for 50 min, then cooled. The resulting yellow precipitate was collected by filtration (0.099 g). Recrystallization of the precipitate from EtOH–H_2O gave yellow fine needles (0.050 g), mp 113—115°C. *Anal.* Calcd for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.14; H, 7.15; N, 14.41.

This compound was identical with a sample of the phenylhydrazone which was derived from the synthetic ethyl integriquinolone, 6-ethoxy-4-methoxy-1-methyl-2-quinolone (**2**)

References and Notes

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8) We confirmed the formation of a mixture of 5- and 7-ethoxyquinolones, when *N*-methyl-*m*-phenetidine was treated with malonic acid.
9) E. Wedekind and E. Fröhlich, *Ber.*, **40**, 1001 (1907).
10) This material was so labile that the sample was decomposed when stored as a solution in $CDCl_3$ at room temperature overnight.
11) Since this oily residue showed two spots on TLC using SiO_2 with a mixed solvent [$CHCl_3$: AcOEt: AcOH=40: 20: 1 (v/v/v)], in the preliminary experiment, the oily mixture obtained from *N*-methyl-*p*-phenetidine (**6**) (0.251 g) was poured into water and extracted with ether. The ethereal solution was extracted with 5% $NaHCO_3$ aq. The aqueous layer was acidified with conc. HCl and extracted again with ether. The ethereal solution was dried over $MgSO_4$ and evaporated to dryness. Preparative TLC of the oily residue on SiO_2 with the mixed solvent [$CHCl_3$: AcOEt: AcOH=40: 20: 1 (v/v/v)] gave two oily components.

The less polar oil (*Rf* 0.38) (0.196 g) was identical with the desired 3-(*N*-methyl-*p*-phenetidino)-propionic acid (**15**).

The more polar oil (*Rf* 0.30) (0.038 g) gave the following physical data. IR ν_{max}^{neat} cm^{-1}: 1730 (CO). ^{1}H-NMR δ: 1.34 (3H, t, J=7.5 Hz, CH_2CH_3), 2.56 (4H, t, J=7.5 Hz, $CH_2CH_2COOCH_2CH_2CO$), 2.80 (3H, s, NCH_3), 3.52 (2H, t, J=7.5 Hz, NCH_2CH_2CO), 3.93 (2H, q, J=7.5 Hz, OCH_2CH_3), 4.30 (2H, t, J=7.5 Hz, OCH_2CH_2), 5.81 (1H, br s, COOH), 6.73 (4H, s, arom. H). These physical data show that this material is 3-[3′-(*N*-methyl-*p*-phenetidino)ethylcarbonyloxy]propionic acid [p-$EtOC_6H_4N(CH_3)CH_2CH_2COOCH_2CH_2COOH$]. Therefore, the crude material was directly hydrolyzed with 1 N NaOH aq. in a large-scale experiment.