Monatshefte für Chemie 119, 1169—1178 (1988)

Monatshefte für Chemie
Chemical Monthly

Natural Product Chemistry. Part 116 [1]. Synthesis of Daurine and Folidine: Two 2(1*H*)-Quinolinone Alkaloids from *Haplophyllum* Species

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(Received 11 December 1987. Accepted 15 January 1988)

Structures of the recently isolated 2(1*H*)-quinolinone alkaloids, daurine and folidine have been confirmed by total synthesis.

(Keywords: Alkaloids; Daurine; Folidine; Haplophyllum; 2(1H)-Quinolinones; Rutaceae; Total synthesis)

Naturstoffchemie. 116. Mitt.: Synthese des Daurins und Folidins, 2(1H)-Chinolinon-Alkaloide aus Haplophyllum Spezies

Die Strukturen der kürzlich aufgefundenen 2(1*H*)-Chinolinon-Alkaloide Daurin und Folidin konnten durch Totalsynthese bestätigt werden.

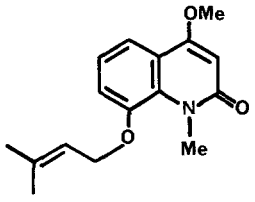
Introduction

Daurine (**1**) and folidine (**2**) are 2(1*H*)-quinolinone alkaloids recently isolated from *Haplophyllum dauricum* and *H. foliosum*, respectively [2, 3]. Molecular structures of these two were elucidated mainly by means of spectroscopic analysis. Continuing our studies on *Rutaceae* alkaloids we have now performed their synthesis in order to confirm these structures and to obtain authentic material which will be useful in our future studies on *Haplophyllum* species. It is noteworthy to state that 2(1*H*)-quinolinones or compounds derived from this basic skeleton have shown various biological activities and some of these have been the subject of extensive pharmacological studies [4]. Hence the synthesis of these compounds will also permit to obtain them in sufficient quantities in order to study their biological/pharmacological activities.

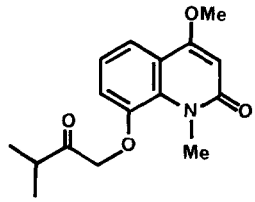
Conventional synthetic pathways leading to 4-hydroxy-2-(1*H*)-quinolinones involve cyclization of malonanilides prepared from the

reaction of an aniline derivative (with required substituents in the benzene ring) with malonic acid or malonic acid derivatives [5–7]. Usually the yields in these cyclizations are rather low and attempts to carry out the synthesis of the title compounds by this manner were unsuccessful. Therefore it was decided to construct the quinoline ring nucleus by a different route and hence 3-hydroxy anthranilic acid (**3**) was chosen as the starting material.

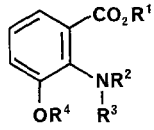
The methods employed herein (see Scheme 1) have resulted in the synthesis of the 2(1*H*)quinolinones **1** and **2** in 18% and 10% overall yields respectively; the yields of the cyclization steps were satisfactorily high (see Experimental).



(1)



(2)



(3) $R^1 = R^2 = R^3 = R^4 = H$

(4) $R^1 = Et$, $R^2 = R^3 = R^4 = H$

(5) $R^1 = Et$, $R^2 = Ac$, $R^3 = R^4 = H$

(6) $R^1 = Et$, $R^2 = R^4 = Ac$, $R^3 = H$

(8) $R^1 = Et$, $R^2 = Ac$, $R^3 = H$, $R^4 = \cdot CH_2$

(9) $R^1 = Et$, $R^2 = Ac$, $R^3 = Me$, $R^4 = \cdot CH_2$

(10) $R^1 = H$, $R^2 = Ac$, $R^3 = Me$, $R^4 = \cdot CH_2$

(12) $R^1 = Et$, $R^2 = Ac$, $R^3 = H$, $R^4 = \cdot CH_2$

(13) $R^1 = Et$, $R^2 = Ac$, $R^3 = H$, $R^4 = \cdot CH_2$

(14) $R^1 = Et$, $R^2 = Ac$, $R^3 = Me$, $R^4 = \cdot CH_2$

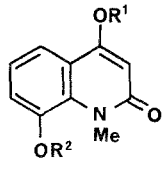
Results and Discussion

Esterification and N-acetylation of 3-Hydroxy anthranilic acid (**3**) were carried out by successive treatment with boiling ethanol in acidic medium and acetic anhydride in pyridine at room temperature. The major product obtained in the latter reaction was found to be the N-acetyl-3-hydroxy ethyl anthranilate (**5**), while the minor constituent isolated in 15% yield was identified as N-acetyl-3-acetoxy ethyl anthranilate (**6**).

The next obvious step was insertion of the appropiate group on the oxygen function in the aromatic ring. This has been possible by treatment of **5** with 1-bromo-3-methyl-2-butene and 1-bromo-3-methyl-2-butanone (prepared by bromination of 2-methylbutanone with bromine in methanol at 0 °C [8]) to produce **8** and **12**, respectively.

Transformations leading to **1** and **2** involved N-methylation, cyclization and O-methylation; cyclization being the crucial step. N-methylation of **8** was achieved with iodomethane in the presence of potassium *tert*-butoxide and a crown ether in refluxing anhydrous ether [9, 10], to yield **9**. Cyclization of **9** (again with potassium *tert*-butoxide in dry ether under reflux) afforded 4-hydroxy-1-methyl-8(3-methyl-2-butenyl)oxy-2(1*H*) quinolinone (**11**). Attempts to attain both steps in one-pot with 2-molar equivalents of potassium *tert*-butoxide yielded a mixture of products, consisting of the N-methylated ester (**9**), its acid (**10**) and the desired quinolinone (**11**), of which **10** predominates. Subsequent O-methylation of **11** was straight forward and performed with ethereal diazomethane in methanol, to yield 4-methoxy-1-methyl-8(3-methyl-2-butenyl)oxy-2(1*H*)-quinolinone (daurine; **1**).

Since N-methylation and cyclization were carried out under strong basic conditions, the carbonyl group of **12** was—prior to these steps—



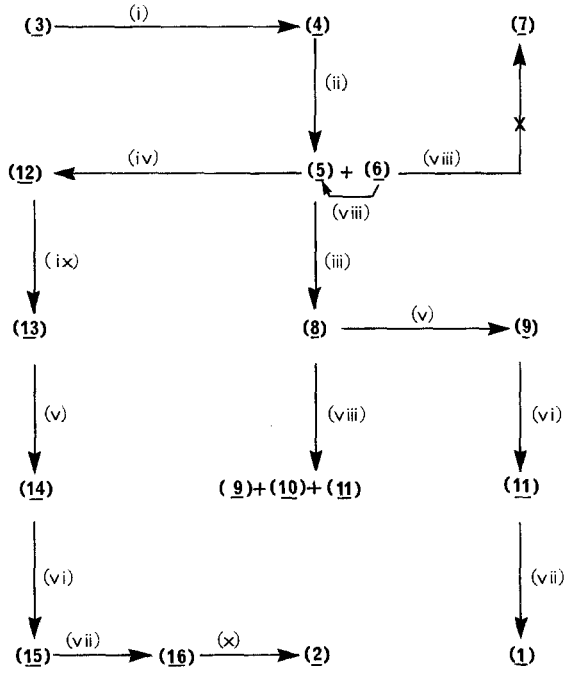
(7) R^1 = H, R^2 = Ac

(11) R^1 = H, R^2 = CH_2

(15) R^1 = H, R^2 = CH_2

(16) R^1 = Me, R^2 = CH_2

Scheme 1



Reagents: (i) ethanol/c.H_2SO_4/100 °C/3hrs; (ii)Ac_2O/Pyridine/room temp./16hrs; (iii) $Me_2C{=}CHCH_2Br$/anh. K_2CO_3/anh.acetone/reflux/2hrs; (iv) $Me_2CHCOCH_2Br$/anh.K_2CO_3/anh.acetone/reflux/2hrs; (v)MeI/^{t}BuOK (1 mol.equivalent)/dicyclohexyl 18crown6/anh.ether/reflux/0.5hrs; (vi) ^{t}BuOK (1 mol.equivalent)/anh.ether/reflux/5min; (vii) CH_2N_2/ether/0.5hrs; (viii)MeI/ ^{t}BuOK (2mol.equivalents)/ dicyclohexyl 18crown6/anh.ether/reflux/1.5hrs; (ix) $HOCH_2CH_2OH$/Me_3SiCl/room temp./15hrs; (x) c.H_2SO_4/acetone/reflux/1.5 hrs.

protected by acetalization with ethandiol in the presence of chlorotrimethylsilane [11]; subsequently N-methylation, cyclization and O-methylation were carried out as above to yield **16**. Deprotection of the carbonyl group of **16** was achieved by treatment with conc. sulphuric acid in acetone [12] to produce the desired 4-methoxy-1-methyl-8(3-methyl-2-oxo butoxy)-2(1*H*)-quinolinone (folidine; **2**).

Synthesis of **2** or any other analogue is thus much simpler if one can protect the phenolic hydroxy group of **5** prior to N-methylation, cyclization and O-methylation; after deprotection any desired side chain can be introduced. This was attempted utilizing **6** as the protected intermediate. When, however, **6** was treated under normal potassium *tert*-butoxide conditions with iodomethane and the crown ether, deacetylation occured to produce **5**, instead of the expected 4-hydroxy-2(1*H*)-quinolinone (**7**) (see Scheme 1).

Acknowledgement

We are grateful to the "Deutsche Forschungsgemeinschaft" for financial support and to the "Heinrich-Hertz-Stiftung" for the award of a fellowship to *GMKBG*.

Experimental

All melting points were determined on *Kofler*-hot stage microscope and are uncorrected. ^{1}H nmr were recorded on a Varian T 60 spectrophotometer in deuteriochloroform as solvent and tetramethylsilane as internal standard (unless otherwise stated). Mass spectra were obtained on a Varian MAT 44 S instrument.

Silica-gel 60 F_{254} (pre-coated aluminium sheets; 0.2 mm thickness; Merck 5549) were used for analytical thin layer chromatography whilst for preparative work, Silica-gel 60 F_{254} (pre-coated plates, 2 mm thickness; Merck 5717 and 0.25 mm thickness; Merck 5715) were employed. Light petroleum refers to the b.p. 30–40° fraction.

3-hydroxy-anthranilic acid 97% (Aldrich Chem. Co.), 1-bromo-3-methyl-2-butene (Fluka AG), and 3-methyl-2-butanone (Janssen Chimica) were used without further purification.

3-Hydroxy ethylanthranilate (**4**)

3-hydroxy anthranilic acid (1.0 g) was heated under reflux in a mixture of dry ethanol (25 ml) and conc. sulphuric acid (10 ml) for 3 h. The reaction mixture was diluted with water (300 ml) and sodium bicarbonate (20 g) added in order to neutralize the solution. The mixture was then extracted with ether (75 ml × 3) and the combined ether layers were washed with saturated sodium chloride solution (50 ml × 2) and dried over anhydrous sodium sulphate. Evaporation of the solvent yielded the crude ethyl ester of 3-hydroxy anthranilic acid as a low melting brown solid, which on recrystallization from chloroform/light petroleum yielded off-white needles (1.145 g; 97%) m.p. 89–91 °C. ^{1}H nmr: δ 7.38 (dd, J = 2 and 8 Hz, 1 H, *Ar*H), 6.88 (dd, J = 2 and 8 Hz, 1 H, *Ar*H), 6.38 (t, J = 8 Hz, 1 H, *Ar*H), 4.26 (q, J = 7 Hz, 2 H, OCH_2CH_3), 1.33 (t, J = 7 Hz, 3 H, OCH_2CH_3).

N-Acetylation of 3-hydroxy ethyl anthranilate (**4**)

The above prepared 3-hydroxy ethyl anthranilate (**4**; 1.145 g) was dissolved in pyridine (1.5 ml) and acetic anhydride (0.75 ml) was added and stirred over night (~ 16 h) at room temperature. Ice was added to the reaction mixture, which was then acidified with dilute hydrochloric acid and extracted with ether (50 ml × 3).

The combined ether layers were washed with sodium chloride solution (50 ml × 2) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure yielded a brown solid (0.901 g), which appeared as one major product together with a second more polar spot on t.l.c. Purification by preparative thin layer chromatography (eluant: 2% methanol in dichloromethane) yielded N-acetyl-3-hydroxy ethyl anthranilate (**5**; 0.74 g; 82%), m.p. 53–54 °C. ^{1}H nmr: δ 11.16 (br, 1 H, NH), 9.86 (s, 1 H, OH), 7.58 (dd, J = 3 and 6 Hz, 1 H, *Ar*H), 7.36–6.90 (m, 2 H, *Ar*H), 4.38 (q, J = 7 Hz, 2 H, OCH_2CH_3), 2.35 (s, 3 H, —$COCH_3$), 1.41 (t, J = 7 Hz, 3 H, OCH_2CH_3). MS: *m/z* (rel. int.) 223 (M^+, 40%), 180 (100), 135 (100), 107 (58), 79 (11). Anal. calcd. for $C_{11}H_{13}NO_4$: C 59.17, H 5.87, N 6.27; found: C 59.53, H 6.01, N 6.30.

The aqueous layer was again extracted with dichloromethane (50 ml × 2); combined dichloromethane layers were washed with sodium chloride solution and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure yielded an off-white solid (0.251 g, 15%) which appeared on t.l.c. to be identical with that earlier observed more polar product. ^{1}H nmr of this solid identified it to be the N-acetyl-3-acetoxy ethyl anthranilate (**6**). ^{1}H nmr: δ 9.03 (br, 1 H, NH), 7.85 (dd, J = 3 and 6 Hz, 1 H, *Ar*H), 7.43–7.06 (m, 2 H, *Ar*H), 4.36 (q, J = 7 Hz, 2 H, OCH_2CH_3), 2.30 (s, 3 H, $COCH_3$), 2.20 (s, 3 H, $COCH_3$), 1.40 (t, J = 7 Hz, 3 H, OCH_2CH_3). MS: *m/z* (rel. int.) 266 (M^+ + 1, 3%), 265 (M^+, 1%), 223 (7), 205 (34), 181 (100), 135 (84), 107 (32), 78 (12). M^+: found, 265.094839; $C_{13}H_{15}NO_5$ requires M, 265.095024.

Attempted-N-methylation and cyclization of **6** *to prepare 4-hydroxy-1-methyl-8-acetoxy 2(1H)-quinolinone* (**7**)

The diacetylated ester (**6**) (0.250 g) was dissolved in anhydrous diethyl ether, potassium *tert*-butoxide (0.225 g) and dicyclohexyl-18 crown 6 (2 mg) were added and heated under reflux. Iodomethane (0.06 ml) was then added and refluxing was continued for further 1.5 h. Water was added, the mixture was then acidified with dilute hydrochloric acid and extracted with ether. The separated organic layer was washed with water and dried over anhydrous sodium sulphate. The product (m.p. 54–55 °C) obtained on evaporation of the solvent and recrystallization from dichloromethane/light petroleum was found to be identical with N-acetyl-3-hydroxy ethyl anthranilate (**5**); (m.p., mixed m.p., t.l.c., and ^{1}H nmr) and not the expected product (**7**).

N-Acetyl-3-(3-methyl-2-butenyl)oxy-ethyl anthranilate (**8**)

The above prepared N-acetyl-3-hydroxy ethyl anthranilate (**5**; 0.123 g) was dissolved in dry acetone (10 ml), and after the addition of anhydrous potassium carbonate (0.25 g) and 1-bromo-3-methyl-2-butene (0.1 ml), was heated under reflux for 2 h. The reaction mixture was filtered, solids were washed with acetone and dichloromethane and the combined filtrates were evaporated under reduced pressure to yield essentially pure **8** as an off-white crystalline solid (0.158 g, 99%). Recrystallization with dichloromethane/light petroleum gave white needles, m.p. 102–104 °C, ^{1}H nmr: δ 7.93 (br, 1 H, NH), 7.50–6.96 (m, 3 H, *Ar*H), 5.46 (t, J = 8 Hz, 1 H, =CH—CH_2), 4.56 (d, J = 8 Hz, 2 H, OCH_2—CH=), 4.33 (q, J = 7 Hz, 2 H, OCH_2CH_3), 2.16 (s, 3 H, —$COCH_3$), 1.80 (s, 3 H, =C—CH_3), 1.75 (s, 3 H, =C—CH_3), 1.36 (t, J = 7 Hz, 3 H, OCH_2CH_3). MS: *m/z* (rel. int.); 291 (M^+, 2%), 223 (28), 181 (100), 135 (45), 107 (12), 69 (39). M^+: found 291.1476425; $C_{16}H_{21}NO_4$ requires M, 291.147059. Anal. calcd. for $C_{16}H_{21}NO_4$: C 65.94, H 7.27, N 4.81; found: C 65.21, H 7.23, N 4.81.

N-Acetyl-N-methyl-3(3-methyl-2-butenyl)oxy ethyl anthranilate (**9**)

N-acetyl-3(3-methyl-2-butenyl)oxy ethyl anthranilate (**8**; 0.155 g) dissolved in anhydrous ether (25 ml) was heated with potassium *tert*-butoxide (0.065 g), dicyclohexyl 18 crown 6 (1 mg). While the reaction mixture was under reflux, iodomethane (0.04 ml) was added and heating continued for a further 0.5 h. After addition of water to the mixture the product was recovered with ether. The ether layers were washed with water and dried over anhydrous sodium sulphate and evaporated under reduced pressure to afford **9** as an off-white oil (0.146 g, 89%). ^{1}H nmr: δ 7.56–7.03 (m, 3 H, *Ar*H), 5.43 (t, J = 8 Hz, 1 H, =C**H**—CH_2—), 4.60 (d, J = 8 Hz, 2 H, O—$\mathbf{CH_2}$—CH=), 4.36 (q, J = 7 Hz, 2 H, OCH_2CH_3), 3.13 (s, 3 H, N—CH_3), 1.76 (br. s, 9 H, $COCH_3$ and =CMe_2), 1.36 (t, J = 7 Hz, 3 H, $OCH_2\mathbf{CH_3}$). MS: *m/z* (rel. int.) 306 (M^+ + 1, 1.5%), 305 (M^+, 1%), 237 (30), 195 (100), 148 (40), 69 (46). M^+: found, 305.162907; $C_{17}H_{23}NO_4$ requires M, 305.162709.

Cyclization of **9** *to 3-hydroxy-1-methyl-8(3-methyl-2-butenyl)oxy-2(1H) quinolinone* (**11**)

The N-methyl derivative **9** (0.140 g) was dissolved in anhydrous ether (10 ml), potassium *tert*-butoxide (0.051 g) added and heated under reflux for 5 min. After acidification with dilute hydrochloric acid (5 ml) the product was recovered in ether. The ether layers were dried over anhydrous sodium sulphate and evaporated to dryness, to yield crude **11** as a pale yellow solid (0.129 g). Purification by preparative thin layer chromatography (eluant: 6% methanol in dichloromethane) yielded pure **11** as white crystalline solid (0.063 g, 53%), recrystallising from methanol as white needles, m.p. 192–193 °C. ^{1}H nmr: δ 7.66 (dd, J = 3 and 7 Hz, 1 H, *Ar*H), 7.30–6.83 (m, 2 H, *Ar*H), 6.16 (s, 1 H, H-3), 5.50 (t, J = 7 Hz, 1 H, = C**H**—CH_2), 4.48 (d, J = 7 Hz, 2 H, O—$\mathbf{CH_2}$CH=), 3.76 (s, 3 H, N—CH_3), 1.83, 1.76 (s, 3 H each, =C Me_2). MS: *m/z* (rel. int.); 259 (M^+, 4%), 191 (100), 162 (24), 148 (19), 121 (8), 69 (100). M^+: found 259.1208237; $C_{15}H_{17}NO_3$ requires M, 259.1208440.

Methylation of **11** *to yield 4-methoxy-1-methyl-8(3-methyl-2-butenyl)oxy-2(1H) quinolinone* (*Daurine*, **1**)

The above prepared 4-hydroxy-2(1*H*) quinolinone derivative (**11**, 0.061 g) was dissolved in methanol (2 ml) and treated with excess ethereal diazomethane, and stirred for 0.5 h. Evaporation of the solvents and purification by preparative thin layer chromatography (eluant: 2% methanol in dichloromethane) yielded daurine (**1**) as a white crystalline solid (0.0533 g, 82%). Recrystallization with dichloromethane/light petroleum gave white needles, m.p. 118–119 °C (lit. [1] m.p.117–118 °C). ^{1}H nmr: δ 7.55 (dd, J = 4 Hz and 9 Hz, 1 H, *Ar*H), 7.30–7.00 (m, 2 H, *Ar*H), 6.03 (s, 1 H, H-3), 5.53 (t, J = 7 Hz, 1 H, =C**H**—CH_2), 4.56 (d, J = 7 Hz, 2 H, OCH_2—CH=), 3.93 (s, 6 H, N-*Me*, O*Me*), 1.80, 1.73 (s, 3 H each, =CMe_2). MS: *m/z* (rel. int.): 273 (M^+, 5%), 205 (100), 190 (14), 174 (12), 91 (15), 69 (33). M^+: found 273.136620; $C_{16}H_{19}NO_3$ requires M, 273.136494.

1-Bromo-3-methyl-2-butanone

3-methyl-2-butanone (21 ml) was brominated in methanol with bromine at 0–10 °C according to the method of *Gaudry* and *Marquet* [8]. The product obtained (20 ml) was found to contain both the 1-bromo isomer (94%) and the 3-bromo isomer (6%) [13]. ^{1}H nmr: δ 4.01 (s, 2 H, CH_2), 3.00 (septet, J = 7 Hz, 1 H, —CH),

1.16 (d, $J = 7$ Hz, 6 H, $CHMe_2$). [Signals due to the 3-bromo isomer are, 2.43 (s, $COCH_3$), 1.86 (s, $2 \times CH_3$).] The product thus obtained was used without further purification.

N-Acetyl-3(3-methyl-2-oxobutoxy)ethyl anthranilate (**12**)

N-acetyl-3-hydroxy ethyl anthranilate (**5**; 0.103 g) was treated with the above prepared ketone, 1-bromo-3-methyl-2-butanone (0.10 ml) under similar conditions employed to prepare **8**. The crude product recovered as a light brown oil was purified by preparative thin layer chromatography (eluant: 6% methanol in dichloromethane) to afford a white crystalline solid (0.101 g, 71%); obtained as white neddles from dichloromethane/light petroleum, m.p. 78–80 °C. ^{1}H nmr: δ 8.61 (br. 1 H, NH), 7.50 (dd, $J = 2$ and 7 Hz, 1 H, *Ar*H), 7.33–6.86 (m, 2 H, *Ar*H), 4.76 (s, 2 H, —OCH_2CO), 4.35 (q, $J = 7$ Hz, 2 H, —$\mathbf{OCH_2CH_3}$), 2.85 (septet, $J = 7$ Hz, 1 H, —$\mathbf{CH}Me_2$), 2.20 (s, 3 H, $COCH_3$), 1.36 (t, $J = 7$ Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.15 (d, $J = 7$ Hz, 6 H, —$CHMe_2$). MS: *m/z* (rel. int.): 307 (M^+, 20%), 265 (48), 222 (16), 179 (100), 148 (84), 134 (54), 106 (29), 71 (18), 65 (23). M^+: found, 307.142950; $C_{16}H_{21}NO_5$ requires *M*, 307.141974.

1,3-Dioxalane derivative of N-acetyl-3(3-methyl-2-oxobutoxy)ethyl anthranilate (**13**)

N-acetyl-3(3-methyl-2-oxobutoxy)ethyl anthranilate (**12**; 0.101 g) was dissolved in ethandiol (2 ml), trimethylchlorosilane (0.20 ml) added, and the mixture stirred for 15 h at room temperature. The resulting reaction mixture was basified with 10% aqueous potassium carbonate solution and extracted with ether (30 ml × 3). The combined ether layers were washed with water, dried over anhydrous sodium sulphate and evaporated under reduced pressure to yield **13** as a white solid (0.144 g, 99%). Recrystallization with dichloromethane/light petroleum yielded white needles, m.p. 103–105 °C. ^{1}H nmr: δ 8.06 (br. 1 H, NH), 7.56–7.00 (m, 3 H, *Ar*H), 4.33 (q, $J = 7$ Hz, 2 H, —$\mathbf{OCH_2CH_3}$), 4.06 (s, 4 H, OCH_2CH_2O), 4.03 (s, 2 H, —OCH_2—), 2.38–1.80 (m, 1 H, $\mathbf{CH}Me_2$), 2.16 (s, 3 H, —$COCH_3$), 1.38 (t, $J = 7$ Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.03 (d, $J = 7$ Hz, 6 H, —$CHMe_2$). MS: *m/z* (rel. int.): 351 (M^+, 0.5%), 180 (5), 115 (100), 87 (16), 71 (14). M^+ found, 351.168038; $C_{18}H_{25}NO_6$ requires *M*, 351.168189.

Preparation and cyclization of N-methyl-derivative (**14**) *and subsequent O-methylation to yield 4-methoxy-2(1H)-quinolinone derivative* (**16**)

These three steps have been carried out in a similar fashion as employed in preparation of **9**, **11** and **1** (as presented earlier).

Preparation of N-methyl derivative (**14**)

Treatment of **13** (0.114 g) with potassium *tert*-butoxide (0.036 g), dicyclohexyl-18 crown 6 (1 mg) and iodomethane (0.03 ml) afforded **14** as a white solid (0.0776 g, 65.5%); recrystallising as needles (m.p. 81–82 °C) from dichloromethane/light petroleum. ^{1}H nmr: δ 7.60–7.00 (m, 3 H, *Ar*H), 4.35 (q, $J = 7$ Hz, 2 H, O—$\mathbf{CH_2CH_3}$), 4.06 (s, 6 H, —OCH_2 and —OCH_2CH_2O—), 3.16 (s, 3 H, N—CH_3), 1.80 (s, 3 H, —$COCH_3$), 1.36 (t, $J = 7$ Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.01 (d, $J = 7$ Hz, 6 H, —$CHMe_2$). MS: *m/z* (rel. int.): 365 (M^+, 0.5%), 320 (1.3), 190 (2), 162 (2.4), 148 (6). 115 (100), 87 (4), 71 (5). M^+ found, 365.184383; $C_{19}H_{27}NO_6$, requires *M*, 365.183839.

Preparation of 4-hydroxy-2(1H)quinolinone derivative (**15**)

The above prepared **14** (0.0776 g) was treated with potassium *tert*-butoxide (0.027 g) to yield **15** as a white solid (0.0578 g, 85%); recrystallising from methanol as white needles, m.p. 234–236 °C. ^{1}H nmr (dimethylsulphoxide—d_6): δ 7.85–7.05 (m, 3 H, *Ar*H), 6.00 (s, 1 H, H-3), 4.03, 4.00 (s each, 6 H, OCH_2CH_2O and OCH_2—), 3.86 (s, 3 H, N—CH_3), 2.15 (m, 1 H, —C**H***Me*$_2$), 1.00 (d, J = 7 Hz, 6 H, —CH*Me*$_2$). MS: *m/z* (rel. int.): 319 (M^+, 5%), 276 (4), 190 (9), 161 (9), 147 (15), 115 (100), 114 (100), 71 (17). M^+ found, 319.1419701; $C_{17}H_{21}NO_5$ requires M, 319.1419740.

Preparation of 4-methoxy-2(1H)quinolinone derivative (**16**)

The above prepared 4-hydroxy-2(1*H*)quinolinone derivative (**15**, 0.057 g) was treated with diazomethane to afford **16**, which on purification by preparative thin layer chromatography yielded a crystalline white solid (0.038 g, 64%); recrystallising from dichloromethane/light petroleum as white needles, m.p. 164–166 °C. ^{1}H nmr: δ 7.86–7.03 (m, 3 H, *Ar*H), 6.06 (s, 1 H, H-3), 4.05 (m, 6 H, OCH_2 and —OCH_2CH_2O—), 3.95 (s, 3 H, N—CH_3), 2.23–1.60 (m, 1 H, —C**H***Me*$_2$), 1.01 (d, J = 7 Hz, 6 H, —CH*Me*$_2$). MS: *m/z* (rel. int.): 333 (M^+, 4%), 204 (12), 174 (8), 115 (100), 71 (8). M^+: found, 333.1584325; $C_{18}H_{23}NO_5$ requires M, 333.157624.

Preparation of desired 4-methoxy-1-methyl-8-(3-methyl-2-oxobutoxy)-2(1H) quinolinone (*Folidine*, **2**)

The quinolinone derivative **16** (0.018 g) was dissolved in acetone (5 ml), 2 drops of concentrated sulphuric acid was added and the mixture heated under reflux for 1.5 h. Water (a few drops), excess solid sodium hydrogencarbonate, and finally dichloromethane (20 ml) were then added to the reaction mixture. The resulting solids were removed by filtration and the organic layer was dried over anhydrous sodium sulphate. After evaporation of the solvents the residue was purified by preparative thin layer chromatography (eluant: 4% methanol in dichloromethane) to yield folidine (**2**) as a crystalline white solid (0.012 g, 77%). Recrystallization from dichloromethane/light petroleum yielded white needles, m.p. 147–148 °C (lit. [3] m.p. 148–149 °C). ^{1}H nmr: δ 7.63 (dd, J = 2 and 7 Hz, 1 H, *Ar*H), 7.26–6.83 (m, 2 H, *Ar*H), 6.03 (s, 1 H, H-3), 4.76 (s, 2 H, —OCH_2CO), 3.96, 3.93 (s, 3 H, each, —NCH_3 and —OCH_3), 2.83 (septet, J = 7 Hz, 1 H, —CH—*Me*$_2$), 1.18 (d, J = 7 Hz, 6 H, —CH*Me*$_2$). MS: *m/z* (rel. int.): 289 (M^+, 54%), 218 (74), 204 (100), 189 (86), 174 (97), 146 (12), 115 (10), 77 (10). M^+ found, 289.131512, $C_{16}H_{19}NO_4$ requires M, 289.131409.

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[13] The ratio was calculated by ^{1}H nmr using the methyl signals at δ 1.16 (1 bromo isomer) and δ 1.86 (3 bromo isomer)