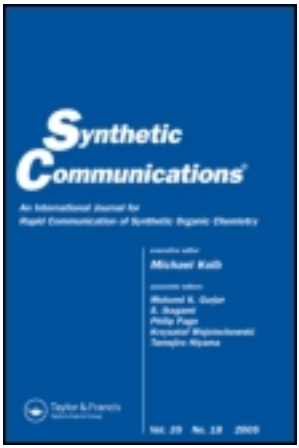

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A Versatile Synthesis of Acridine-1,9-Diones

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A VERSATILE SYNTHESIS OF ACRIDINE-1,9-DIONES

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Abstract: Alkylation of ethyl 2-(4-oxo-1,4-dihydroquinolin-2-yl)acetate by Michael addition with various alkenes has been carried out. The C-α alkylated intermediates so formed can be cyclized with hot polyphosphoric acid to acridine-1,9-diones.

Some time ago[1] we reported an efficient synthesis of **1a** and found that reaction with malonic acid derivatives was accompanied by cyclization onto C-3 or N to give **2** and **3**. Compound **1a** appeared to be a useful precursor to tricyclic systems but these malonate reactions were somewhat limiting. We have therefore studied the attachment of other carbon fragments to Cα of **1a** through Michael addition of α,β-unsaturated esters, and the subsequent cyclization of these intermediates. The direction of this latter ring closure is interesting but the sequence is most useful as a source of acridine-1,9-diones. This system

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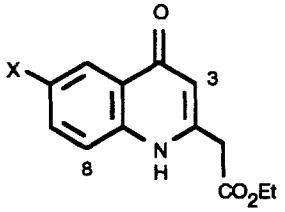
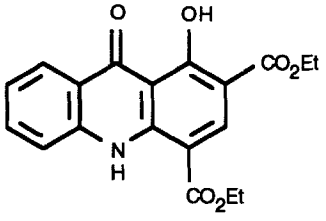
is of continuing interest, for example as the precursor of a new class of anti-malarial compound[2] and our method represents an improvement on the published one.



1 a X = H
1 b X = Cl



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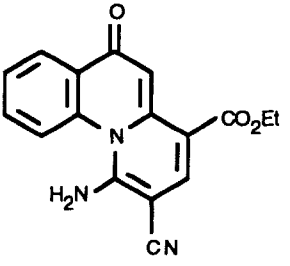

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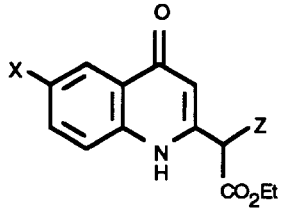
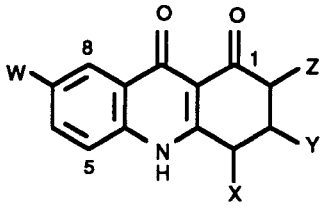
Results and Discussion

The Michael additions were carried out in dimethyl sulfoxide on the sodium salt of **1a**, preformed by reaction with sodium ethoxide in ethanol. A range of alkenes was employed and the use of 1.5 mol equivalents of ethoxide, in DMSO at room temperature gave good yields of the desired C-alkylated intermediates **4**. These were cyclized to acridinediones **5** with polyphosphoric acid (PPA) at 110°, though the times required for each step depended on the particular substrate. In some cases an ester group was lost, usually that derived from **1a**. The ester group in this orientation was quite labile and old 'wet' PPA favored this occurrence.



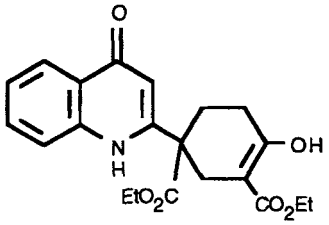


			X	Y	Z
4 a	Z = $CH_2CH_2CO_2Et$	**5 a**	CO_2Et	H	H
b	Z = $CH(Me)CH_2CO_2Et$	**b**	CO_2Et	Me	H
c	Z = $CH(Ph)CH_2CO_2Me$	**c**	H	Me	H
d	Z = $CH(CO_2Et)CH_2CO_2Et$	**d**	H	Ph	H
e	Z = $CH(Me)CH(CO_2Et)_2$	**e**	H	Me	CO_2Me
f	Z = $CH(Me)CH(CO_2Me)_2$	**f**	H	$C_6H_3Cl_2$-2,4	H
g	Z = $CH{=}C(CO_2Et)_2$			W = H except **f** (Cl)	
h	Z = $CH(C_6H_3Cl_2$-2,4)CH_2CO_2Et				
	X = H except **h** (Cl)				

Ethyl acrylate gave **4a** in 0.5 h which was cyclized to **5a** in hot PPA in 16 h. Likewise, ethyl crotonate gave **4b** (12 h) and **5b** (40 h) respectively, while reaction for 3 days resulted also in loss of the ester function derived from **1a** to give **5c**. Similarly, methyl cinnamate gave **4c** (3 h) and **5d** (16 h), both in high yield.

The desired Michael intermediates, mostly oils, were usually readily isolated in good yield. A solid byproduct was obtained during chromatographic purification of **4a**. This was assigned structure **6** which can be rationalized as the product of dialkylation of **1a** with ethyl acrylate followed by intramolecular cyclization. A surprising feature was that it exists entirely as the enol form in chloroform [^{1}H nmr peaks for NH (δ 10.4) and OH (δ 12.17), while the ^{13}C nmr spectrum contained no CH group at δ <100 ppm].

Where the intermediate could cyclize to give an additional 5- or 6-membered ring, the former was preferred and occurred onto N-1.



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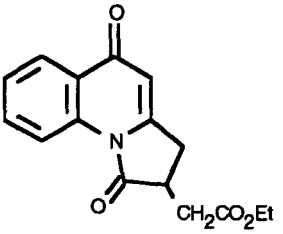

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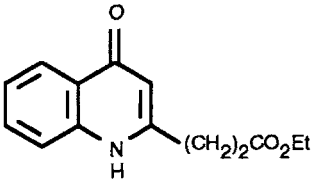

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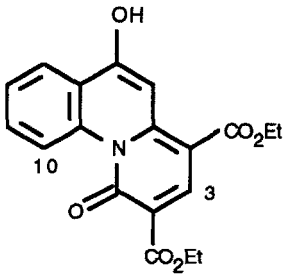

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Thus, **1a**, with diethyl maleate, 1 mol equivalent of ethoxide and a 0.5 h reaction time, gave intermediate **4d** in good yield and this was cyclized in hot PPA in 24 h, with the loss of one ester group, to give **7**. This result is consistent with a previous finding that thermal cyclization of **8** occurred readily onto N-1.[3]

In an attempt to obtain a derivative of **5** containing a useful 2-substituent, **1a** was reacted with diethyl ethylidenemalonate. This proceeded normally and **4e** was formed in 0.5 h. PPA treatment for 16 h was accompanied by loss of one ester group. Unfortunately, this was the one at C-2 as **5b**, identical to that obtained from ethyl crotonate above, was the product. Dimethyl ethylidenemalonate also gave the desired intermediate **4f**. In this case, PPA cyclization was accompanied by partial loss of both ester functions according to nmr and mass spectra, so that an inseparable mixture of **5b** and **5e** resulted.

^{1}H Nmr provided uneqivocal evidence for the direction of the ring closures. The singlet at *ca* 6 ppm for H-3 in **1a** was absent in compounds **5**, while **7** was characterized by a marked downfield shift for the signal corresponding to H-8 in **1a**.

In contrast to the formation of **4e** and **4f**, reaction of **1a** with the related diethyl ethoxymethylenemalonate (EMME) provided the lone case of 6-membered ring formation onto N-1. The red compound isolated from the basic Michael conditions was assigned the ring structure **9**. The presence of the N-CO function was again inferred from the substantial downfield shift for the H-10 signal. The difference between this and the other Michael additions is that the presumed immediate product, **4g**, which was not detected, contains a C=C unit which somehow particularly favors ring closure onto N-1. Compound **9** was a probable intermediate in the previous thermal reaction of **1a** with EMME,[1] though it could not be detected. Now, as expected, **9** was readily thermally isomerized to the previously isolated acridone **2**.

To illustrate the utility of this synthesis of acridinediones, we synthesized **5f**, the precursor of the most active member of a new class of antimalarial agents,[2] in three steps, in good yield, from readily available starting materials. Thus *p*-chloroaniline was converted to **1b** (82%). This with ethyl 2,4-dichlorocinnamate (obtained by standard condensation reaction from 2,4-dichlorobenzaldehyde and ethyl acetate[4] (65%)) gave **4h** (95%) which cyclized in PPA (24 h), with loss of ester group to **5f** (96%). This is simpler than the published method.

This paper illustrates a useful general route from a readily obtained quinoline derivative to tricyclic compounds, particularly **5**. The scheme is versatile with respect to the alkene component in the Michael

reaction, and it is likely that it will also be quite general for substituted anilines.

Experimental

Nmr spectra were run on a Bruker AM 300 spectrometer, in $CDCl_3$ unless stated otherwise. In ^1H spectra, chemical shifts for benzenoid proton signals refer to single protons unless otherwise indicated. Multiplicities alone are recorded; ortho coupling constants were typically ≈8 Hz. Proton-coupled carbon spectra were used to determine numbers of protons attached to the various carbons. Electrospray mass spectra were obtained on a VG Bio-Q triple quadrupole mass spectrometer using a water/methanol/acetic acid (50:50:1) mobile phase. Chromatography was carried out on silica gel..

*Synthesis of **1a** and **1b.*** Compound **1a** was prepared as previously described.[1] The same method gave **1b** in 82% yield, mp 241-242° (from ethanol). ^1H nmr δ 0.93 (t, J = 7 Hz, 3 H), 3.33 (s, 2 H), 3.85 (q, J = 7 Hz, 2 H), 5.83 (s), 7.34 (d), 7.53 (dd, J = 8, 2.3 Hz), 8.29 (d, J = 2.3 Hz). ^{13}C nmr (DMSO-d_6) δ 13.6 (CH_3), 38.8 (CH_2), 61.2 (CH_2), 109.9 (CH), 119.8 (CH), 124.3 (CH), 125.5 (C), 128.7 (CH), 131.6 (CH), 138.6 (C), 145.6 (C), 168.2 (C), 176.6 (C).

Procedure for Michael addition. Sodium ethoxide in dry ethanol (0.5 M solution, 1.5 mol equivalents unless otherwise stated) was added to a solution of compound **1** in ethanol (5 ml/0.1 g). The mixture was stirred at rt for 20 min. and the ethanol was removed under reduced pressure. Dry dimethyl sulfoxide (5 ml/0.1 g **1**) was added followed by 1 mol equivalent of the alkylating agent and the solution was stirred at room temperature for the specified time. Cold water was added, the mixture was neutralized

with 12% hydrochloric acid. Where a solid was formed, this was filtered off, otherwise the crude product was isolated by extraction with chloroform. Purification was by column chromatography, C, or recrystallization.

Procedure for polyphosphoric acid cyclization. The substrate was mixed with five times its weight of PPA and the mixture was heated at 110-120° for the specified time. Ice-water was added to the cooled mass, the pH was taken to 5-6 with 10% sodium hydroxide solution. With one exception, the product separated as a solid and was filtered off. The oily **7** was extracted with chloroform and the extract was dried and concentrated to give the crude product.

In these ways the following were prepared.

Ethyl 4,9-Dioxo-1,2,3,4,9,10-hexahydroacridine-4-carboxylate (**5a**). The intermediate **4a** was obtained in 48% yield from ethyl acrylate, 0.5 h, (C, EtOAc/hexane/EtOH, 6:3:1, R_f 0.6), mp 230-231°. ^{1}H nmr δ 1.15 (t, J = 7 Hz, 6 H), 2.21-2.45 (m, 4 H), 3.83 (t, J = 7 Hz, 1 H), 4.03 (q, J = 7 Hz, 2 H), 4.12 (dq, 2 H), 6.30 (s), 7.31 (m, 1 H), 7.5 (m, 2 H), 8.32 (d). ^{13}C nmr δ 13.9 (CH_3), 14.0 (CH_3), 27.4 (CH_2), 31.5, (CH_2), 48.6 (CH), 60.6 (CH_2), 61.8 (CH_2), 108.6 (CH), 118.4 (CH), 123.9 (CH), 125.2 (C), 125.5 (CH), 132.1 (CH), 140.2 (C), 149.7 (C), 171.2 (2 x C), 178.8 (C). ESMS: m/z 332 (M+1).

Compound **4a** with PPA for 16 h gave **5a** (78%), mp 223-224° (from EtOH) (Found: C, 67.2; H, 5.5; N, 4.8. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%). ^{1}H nmr (DMSO-d_6) δ 1.19 (t, J = 7 Hz, 3 H), 2.38-2.49 (m, 4 H), 4.10 (br s, 1 H), 4.18 (q, J = 7 Hz, 2 H), 7.38 (t), 7.53 (d), 7.70 (t), 8.08 (d). ^{13}C nmr (DMSO-d_6) δ 14.1 (CH_3), 24.0 (CH_2), 35.3 (CH_2), 44.2 (CH), 61.7 (CH_2), 113.6 (C), 118.4 (CH), 124.7 (CH), 125.9 (CH),

127.3 (C), 132.7 (CH), 138.3 (C), 156.2 (C), 170.1 (C), 173.9 (C), 191.9 (C).

Diethyl 2-Hydroxy-5-(4-oxo-1,4-dihydroquinolin-2-yl)cyclohexene-1,5-dicarboxylate (**6**). This was isolated in 16% yield from the same reaction that produced **4a** above (C, EtOAc, R_f 0.5), mp 158-160° (from EtOAc) (Found: C, 65.3; H, 5.9; N, 3.7. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%).^{1}H nmr δ 1.19 (t, *J* = 7 Hz, 3 H), 1.29 (t, *J* = 7 Hz, 3 H), 2.25-2.50 (m, 4 H), 2.68 + 3.16 (d + d, *J* = 15 Hz, 2 H), 4.14-4.25 (m, 4 H), 6.34 (s), 7.32 (t), 7.45 (d), 7.60 (t), 8.29 (d), 10.4 (br s, 1 H), 12.17 (s, 1 H). ^{13}C nmr δ 13.8 (CH_3), 14.1 (CH_3), 26.2 (CH_2), 27.8 (CH_2), 29.6 (CH_2), 49.4 (C), 60.7 (CH_2), 62.2 (CH_2), 95.1 (C), 107.7 (CH), 118.3 (CH), 123.9 (CH), 124.7 (C), 125.4 (CH), 132.2 (CH), 140.4 (C), 151.3 (C), 170.4 (C), 171.5 (C), 172.3 (C), 178.9 (C). ESMS: m/z 386 (M+1).

Ethyl 3-Methyl-4,9-dioxo-1,2,3,4,9,10-hexahydroacridine-4-carboxylate (**5b**). (a) Intermediate **4b** was obtained in 81% yield as a mixture of two diastereomers (1:1) from ethyl crotonate, 12 h, (C, EtOAc/hexane/EtOH, 6:3:1, R_f 0.6). ^{1}H nmr δ 0.95 + 1.06 (d + d, *J* = 7 Hz, 3 H), 1.12-1.26 (m, 6 H), 2.1-2.5 (m, 1 H), 2.78 (m, 2 H), 3.54 + 3.57 (d, *J* = 7 Hz, 1 H), 3.9-4.2 (m, 4 H), 6.28 (s), 7.24 (m), 7.31-7.56 (m, 2 H), 8.34 (d), 10.44 + 10.45 (s + s, 1 H). ^{13}C nmr δ 13.9, 14.0 (CH_3), 17.3, 18.2 (CH_3), 33.7, 34.1 (CH_2), 38.2, 39.1 (CH), 54.3, 54.6 (CH), 60.7, 61.9 (CH_2), 110.3 (CH), 117.9 (CH), 123.9 (CH), 125.2 (C), 125.8 (CH), 132.1 (CH), 139.7, 139.8 (C), 147.4, 147.5 (C), 171.6, 171.9 (C), 178.6 (C). ESMS: m/z 346 (M+1).

(b) Intermediate **4e** was obtained in 74% yield as a mixture of two diastereomers (1:1) from diethyl ethylidenemalonate, 0.5 h , (C, EtOAc, R_f 0.6). ^{1}H nmr δ 1.0-1.2 (m, 12 H), 3.02 (br s, 1 H), 3.37 + 3.59 (d + d, *J* 4.4 Hz, 1 H), 3.83-4.20 (m, 7 H), 6.39 (s), 7.24-7.29 (m, 1 H), 7.49-7.63 (m, 2

H), 8.29-8.33 (m, 1 H). ESMS: m/z 418 (M+1).

Compounds **4b** (40 h) or **4e** (16 h) with PPA each gave **5b** (diastereomers) in >70% yield, mp 227-228° (from EtOH) (Found: C, 68.2; H, 5.4; N, 4.8. $C_{17}H_{17}NO_4$ requires C, 68.2; H, 5.7; N, 4.7%). ^{1}H nmr (DMSO-d_6) δ 1.04-1.21 (m, 6 H), 2.16-2.96 (m, 3 H), 3.88-3.97 (m, 1 H), 4.16 (br q, 2 H), 7.34 (m, 1 H), 7.52 (m, 1 H), 7.65 (m, 1 H), 8.09 (m, 1 H). ^{13}C nmr (DMSO-d_6) δ 14.2 (CH_3), 18.5 (CH_3), 19.3 (CH), 29.9 (CH_2), 42.5 (CH), 61.4 (CH_2), 113.0 (C), 118.4 (CH), 124.7 (CH), 125.9 (CH), 127.1 (C), 132.7 (CH), 138.3 (C), 160.2 (C), 170.3 (C), 173.8 (C), 193.1 (C). ESMS: m/z 300 (M+1).

3-Methyl-1,2,3,4,9,10-hexahydroacridine-1,9-dione (**5c**). From intermediate **4b** with PPA for 72 h, 91%, mp 273° (from EtOH), which could not be freed of a trace impurity. ^{1}H nmr δ 1.23 (d, J = 7 Hz, 3 H), 2.46-2.58 (m, 2 H), 2.86-3.04 (m, 2 H), 3.42 (d, J = 17.4 Hz, 1 H), 7.62 (t), 7.91 (t), 8.34-8.37 (m, 2 H). ^{13}C nmr (DMSO-d_6) δ 20.7 (CH_3), 27.7 (CH), 36.2 (CH_2), 47.0 (CH_2), 116.7 (C), 118.3 (CH), 124.4 (CH), 125.8 (CH), 126.9 (C), 132.5 (CH), 138.5 (C), 160.3 (C), 176.2 (C), 193.4 (C). ESMS: m/z 228 (M+1).

3-Phenyl-1,2,3,4,9,10-hexahydroacridine-1,9-dione (**5d**). Intermediate **4c** was obtained in 76% yield as a mixture of two diastereomers (2:1) from methyl cinnamate, 3 h, (C, EtOAc, R_f 0.5), mp 80-82° (Found: C, 69.8; H, 6.2; N, 4.0. $C_{23}H_{23}NO_5$ requires C, 70.2; H, 5.9; N, 3.6%). ^{1}H nmr δ 0.93-1.22 (m, 6 H), 2.65 + 2.80 (m, 2 H), 3.36 + 3.39 (s, 3 H), 3.77-4.18 (m, 5 H), 6.21 + 6.50 (s), 7.08-7.61 (m), 7.31-7.56 (m, 8 H), 8.38 + 8.41 (d).

This with PPA for 16 h gave **5d** (90%), mp 268-269° (from EtOH) (Found: C, 74.0; H, 5.4; N, 4.2. $C_{19}H_{15}NO_2.H_2O$ requires C, 74.3; H, 5.6;

N, 4.6%). The compound was too insoluble for satisfactory nmr. ESMS: m/z 290 (M+1).

7-Chloro-3-(2,4-dichlorophenyl)-1,2,3,4,9,10-hexahydroacridine-1,9-dione (**5f**). Intermediate **4h** was obtained in 95% yield as a mixture of two diastereomers from **1b** and ethyl 2,4-dichlorocinnamate[4] [mp 48-50° (lit.[5] mp 53.5°)], 3 h, mp 85-86° (from EtOAc) ^{1}H nmr δ 0.95-1.05 (m, 6 H), 2.2-2.3 (m, 1 H), 2.70 (br s, 2 H), 3.8-4.0 (m, 4 H), 4.3, (br s, 1 H), 6.37 (s), 7.19 (dd, J = 8, 1.5 Hz, 1 H), 7.27 (d, J = 8 Hz, 1 H), 7.36 (d, J = 1.5 Hz, 1 H), 7.55-7.61 (m, 2 H), 8.36 (d, J = 1.3 Hz, 1 H). ESMS: m/z 510 (100%), 511 (28), 512 (100), 513 (27), 514 (35), 515 (9), all (M+1).

This with PPA for 24 h gave **5f** (96%), mp 304-306° (after trituration with EtOH) (lit.[2] mp 308-310°). ESMS: m/z 392 (100%), 393 (26), 394 (98), 395 (23), 396 (33), 397 (11), 398 (8), all (M+1).

*Reaction of **1a** with Dimethyl ethylidenemalonate.* Intermediate **4f** was obtained in 67% yield as a diastereomeric mixture, 0.5 h , mp 69-70° (C, EtOAc, R_f 0.6). ^{1}H nmr δ 1.0 + 1.14 (d + d, J = 6.9 Hz, 3 H), 1.20-1.27 (m, 3 H), 3.00 (br s, 1 H), 3.40-3.77 (m, 5 H), 4.03-4.13 (m, 2 H), 6.30 (s), 7.29-7.58 (m, 3 H), 8.34 (d). ^{13}C nmr δ 13.9 (CH_3), 15.1 (CH_3), 35.9 (CH), 36.8 (CH), 52.6 (CH_3), 52.9 (CH), 62.1 (CH_2), 110.4 (CH), 118.0 (CH), 124.1 (CH), 125.2 (C), 125.8 (CH), 132.2 (CH), 139.8 (C), 146.8 (C), 168.0 (C), 168.7 (C), 171.3 (C), 178.6 (C).

This with PPA for 16 h gave a solid mixture of compounds **5b** and **5e**. ^{1}H nmr (DMSO-d_6) contained δ 1.22 (t) + 4.15-4.21 (m) for ethyl ester, 3.70 (s) + 3.72 (s) for methyl ester and no peak in region 4.2-7.3. ESMS: m/z 286 (M+1, **5e**), 300 (M+1, **5b**).

Ethyl (1,5-Dioxo-1,2,3,5-tetrahydropyrrolo[1,2-a]quinolin-2-yl)acetate (**7**). Intermediate **4d** was obtained in 72% yield as a mixture of two

diastereomers (2:1) from diethyl maleate, with one mol equivalent of ethoxide for 0.5 h, (C, EtOAc, R_f 0.6). ^{1}H nmr δ 0.95-1.23 (m, 9 H), 2.49-2.85 (m, 2 H), 3.70 (m, 1 H), 3.89-4.15 (m, 6 H), 4.25 (m, 1 H), 6.32 + 6.37 (s), 7.20-7.31 (m), 7.52-7.62 (m, 2 H), 8.29 (d). ^{13}C nmr δ 13.9 (CH_3), 33.8, 33.9 (CH_2), 43.0, 43.1 (CH), 50.4, 50.5 (CH), 60.8, 61.3, 61.8 (CH_2), 108.8, 109.1 (CH), 118.6, 118.7 (CH), 124.1, 124.2 (CH), 124.8 (C), 125.1, 125.4 (CH), 132.2 (CH), 140.3 (C), 148.0, 148.1 (C), 169.2, 169.8 (C), 170.7, 170.8 (C), 172.1, 172.2 (C), 178.5 (C). ESMS: m/z 404 (M+1).

This with PPA for 16 h gave **7**, 72%, C (EtOAc, R_f 0.7) (Found: C, 66.9; H, 5.6; N, 4.7. $C_{16}H_{15}NO_4$ requires C, 67.4; H, 5.3; N, 4.9%). ^{1}H nmr δ 1.19 (t, J = 7 Hz, 3 H), 2.9-3.03 (m, 3 H), 3.21-3.45 (m, 2 H), 4.11 (q, J = 7 Hz, 2 H), 6.23 (s), 7.47 (t), 7.67 (t), 8.30 (d), 9.05 (d). ^{13}C nmr δ 14.0 (CH_3), 29.5 (CH_2), 34.8 (CH_2), 36.8 (CH), 61.3 (CH_2), 108.9 (CH), 117.8 (CH), 125.3 (C), 126.3 (CH), 126.5 (CH), 133.0 (CH), 136.6 (C), 153.3 (C), 170.6 (C), 176.5 (C), 178.9 (C).

Diethyl 6-Hydroxy-1-oxo-1H-benzo[c]quinolizine-2,4-dicarboxylate (**9**). The Michael reaction of **1a** with diethyl methoxyethylenemalonate for 16 h gave the product as a red solid, mp 176-178° (from EtOAc/hexane) in 87% yield (Found: C, 63.9; H, 4.6; N, 3.6. $C_{19}H_{17}NO_6$ requires C, 64.2; H, 4.8; N, 3.9%). ^{1}H nmr δ 1.27 (t, J = 7 Hz, 3 H), 1.38 (t, J = 7 Hz, 3 H), 4.21 (q, J = 7 Hz, 2 H), 4.38 (q, J = 7 Hz, 2 H), 7.40-7.51 (m, 2 H), 8.13 (d), 8.53 (s), 8.83 (s), 9.22 (d).^{13}C nmr δ 14.2 (CH_3), 14.4 (CH_3), 60.9 (CH_2), 61.0 (CH_2), 99.9(CH), 100.3, 107.0, 121.1, 122.5(CH), 122.7(CH), 126.7(CH), 129.7(CH), 136.9, 144.6(CH), 150.9, 161.3, 161.8, 165.5, 165.8.

A sample, when boiled in diphenyl ether for 1 h was converted in high yield to **2**, mp identical with a previous sample.

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