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Synthesis of Some Acridone Alkaloids and Related Compounds

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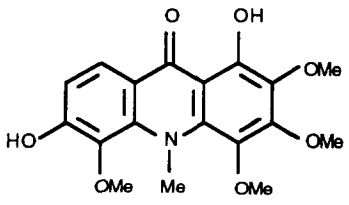
Abstract: An efficient Pd/C aromatization of 1,2,3,4,9,10-hexahydroacridine-1,9-diones to 1-hydroxyacridones is reported. The previously reported four-step synthesis of the diones has been extended to give a number of methoxy substituted derivatives and the aromatization reaction, along with hydrobromic acid demethylation, provides a useful route to various methoxy and hydroxy substituted acridones. © 1997 Published by Elsevier Science Ltd.

INTRODUCTION

The anticancer properties of glyfoline[1] **1** and acronycine[2] **2** focussed attention on the acridone alkaloids. Other members of the class, mostly highly oxygenated derivatives of the acridone skeleton, have shown a range of physiological activities including antimalarial,[3] antiviral[4] and antibiotic[5] properties. Recently there has been an upsurge in the isolation of members of this class from plant sources.[6] The range of physiological effects is intimately affected by the nature and position of the hydroxy and methoxy (henceforth referred to as oxy) substituents. For example, it has been found that the 1-hydroxy, 6-hydroxy and N-methyl groups are necessary for anticancer activity in derivatives of glyfoline.[7] Because of this link between activity and substitution pattern, and because of the interest in the class, synthetic methods which lead to specifically derivatized acridones are desirable. This paper reports on a new method, with generally good yields, applicable to the incorporation of various oxy substituents.



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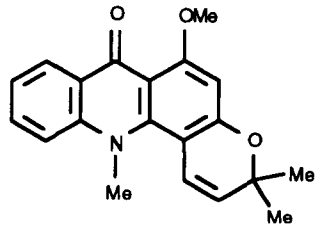

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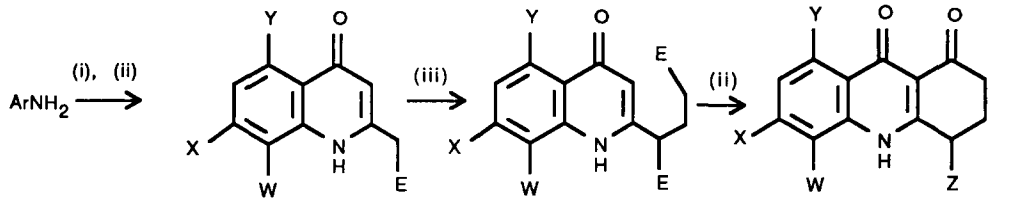
RESULTS AND DISCUSSION

We recently published the synthesis of tetrahydroacridine-1,9-dione **5a** shown in Scheme 1.[8] The readily prepared quinolone derivative **3a** underwent Michael addition with various activated esters (ethyl acrylate is



3	W	X	Y
a	H	H	H
b	MeO	H	H
c	H	MeO	MeO
d	MeO	H	MeO

4	W	X	Y	Z
a	H	H	H	E
b	MeO	H	H	E
c	MeO	H	H	H
d	H	MeO	MeO	E
e	H	MeO	MeO	H
f	MeO	H	MeO	E

E = CO_2Et. (i) $(ECH_2)_2CO$ (ii) PPA (iii) CH_2=CH-E.

Scheme 1

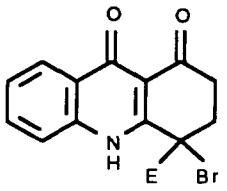
illustrated) and the intermediate **4a** was cyclised in hot polyphosphoric acid (PPA) to give **5a**. The 4-ester group could be retained or lost depending on the severity of the cyclization conditions.

This reaction has now been extended to analogues of **5a**, of interest as described below, and further developed to include their aromatization. Two methods were investigated for the aromatization of **5a**. Reaction with bromine was rapid. The intermediate, probably **6**, readily lost hydrogen bromide in basic conditions, milder than those devised for the change from tetralone to naphthol,[9] to give the aromatized **7a**. However, it was difficult to prevent at least traces of brominated products from also being formed. The alternative method was more satisfactory; this involved heating the dione with one-third of its weight of 10% palladium/carbon in diphenyl ether.[10] The reaction time was important as it was possible again to control whether the 4-ester group was retained or lost. Thus **5a** gave **7a** or the alkaloid **7b**.[11] This latter was N-methylated to give the known **7c**.[11] The palladium aromatization method was general and was used for preparation of the remaining **7** discussed below.

While acridonecarboxylic acids have not been found within the natural alkaloids, the incorporation of this derivatizable function into the synthetic scheme may have valuable advantages in future syntheses of more complex derivatives of the class.

As introduced above, oxy derivatives are of particular interest and we have investigated the applicability of the sequence to their synthesis. When *o*-methoxyaniline was reacted with ethyl acrylate according to Scheme 1, and the product aromatized, control over ester loss in both the cyclization and aromatization steps was achieved and **5b**, **5c**, **7d** and **7e** were obtained depending on conditions. This sequence produced a 1,5-dioxy substitution pattern, of interest since it has been deduced that 1,5-dihydroxy substitution is necessary for antiviral activity.[12] To illustrate that this substitution is accessible, demethylation of **7d** or **7e** with hot hydrobromic acid (with concomitant loss of the ester group from **7d**) gave the dihydroxy compound **7f**.

The synthesis outlined necessarily leads to a 1-hydroxyacridone and an oxy function in this position is



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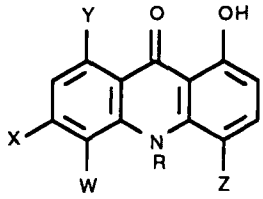


7

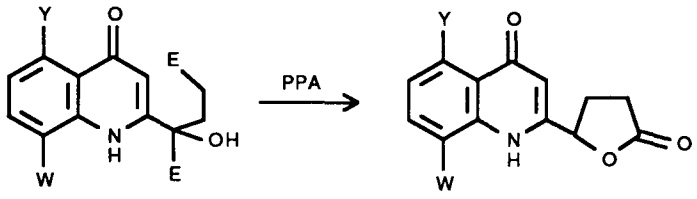
	W	X	Y	Z	R
a	H	H	H	E	H
b	H	H	H	H	H
c	H	H	H	H	Me
d	MeO	H	H	E	H
e	MeO	H	H	H	H
f	HO	H	H	H	H
g	H	MeO	MeO	E	H
h	H	MeO	MeO	H	H
i	H	HO	HO	H	H
j	H	MeO	HO	H	Me
k	H	HO	HO	H	Me
l	MeO	H	MeO	E	H
m	MeO	H	MeO	H	H

characteristic of the acridone alkaloids. However, these usually also contain a 3-oxy substituent and this cannot be incorporated into the starting unsaturated ester for the sequence of Scheme 1. But, the general nature of the synthesis allows this substitution pattern to be incorporated in the starting amine. Thus 3,5-dimethoxyaniline with ethyl acrylate according to Scheme 1, gave **5d** and **5e**. Then aromatization of the former gave acridones **7g** or **7h**, containing the natural 1,3-dioxy pattern and an 8-hydroxy group. This is an interesting substituent combination and only a few alkaloids with the 1,8-dioxy pattern have been described.[11,13] Again, retention of the ester function was optional. Demethylation of either **7g** or **7h** gave **7i**; then methylation gave **7j**, which illustrated the known lower reactivity of hydroxy groups peri to the acridone carbonyl function,[14] and a final demethylation gave the alkaloid **7k**.[11]

As a further illustration of the general nature of the reaction, 2,5-dimethoxyaniline was subjected to the same reaction sequence to produce the non-natural 1,4,8-trioxy pattern of **7l** and **7m**.

Throughout, it was found best to use methoxy substituted starting materials. A procedure for the preparation of the 7-benzyloxy derivative of **3** was devised but the benzyl group did not survive PPA treatment in the attempted preparation of the appropriate **5** and the product was not identified.

While the sequence described above was general, an unexpected side-reaction occurred with both of **3b** and **3d**, i.e., when an 8-methoxy group was present. As well as the target products **4b** and **4d**, appreciable quantities of **8a** and **8b**, respectively, were formed. These had very similar R_f values to **4b** and **4d** but were partially



8 **9**

a W = MeO, Y = H

b W = Y = MeO

separated by chromatography and then **8b** could be crystallized. Most work was carried out on **3d** and the structure of **8b** was assigned from NMR (C-α had no attached hydrogen), IR (broad OH as well as sharp NH peaks), ESMS and microanalytical data, and confirmed by a crystal structure determination (Figure 1). Though not highly accurate because of poor crystal quality and disorder in the crystal, the result is unambiguous regarding the structure about C-α(C11). Bond lengths and angles are similar to those for comparable structures. The 2-(ethoxycarbonyl)ethyl chain is extended with torsion angles C11-C12-C13-C14 167(2)°, C12-C13-C14-O15 123(2)°, C13-C14-O15-C16 170(2)° and C14-O15-C16-C17 136(2)°. In the other ester group the chain C11-C18-O19-C20 is also extended, with torsion angle -174(2)°, whereas the grouping C18-O19-C20-C21 is in a *gauche* orientation with torsion angle -90(2)°. The short intermolecular distance of 2.57(1) Å between two adjacent oxygens, O11...O1 (0.5-x, -0.5 +y, 0.5-z), is indicative of hydrogen bonding. These interactions link the molecules into infinite spirals along the crystal *b* axis. There is also a close intermolecular contact of 2.960(5) Å between O14...O14 (1-x, y, 0.5-z) but all other contacts in the crystal are normal. The origin of these tertiary alcohols is unknown.

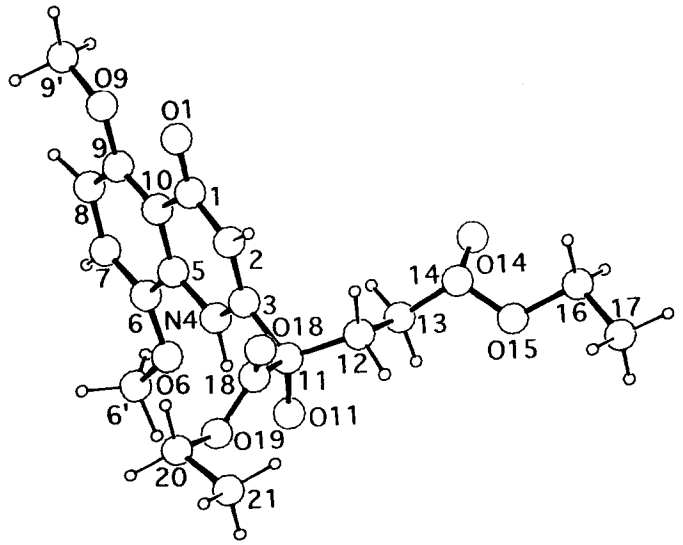
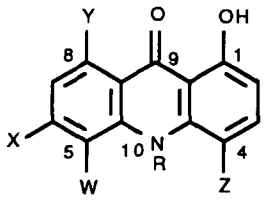


Figure 1. ORTEP[15] drawing of **8b** showing the atomic numbering used in the crystallographic work. The C symbols for the carbon atoms have been omitted.

When reacted in PPA, compounds **8a** and **8b** also underwent a cyclization but the products were assigned structures **9a** and **9b**. From the NMR spectra, C-α and Cα-H were at sufficiently low fields to suggest attachment of C-α to O, H-3 was present and there were no ester groups. ESMS and microanalysis were also in accord with these structures. Intramolecular cyclization of **8** to the 5-membered lactone, with loss of the C-α ester, is apparently the preferred reaction.

^{13}C NMR spectra have been useful in characterizing acridone alkaloids and data for the present compounds are collected in Table 1. Assignments are based on literature values though some discrepancies were noted. In the 1,3-dioxy situation, C-2[16] and C-4[17] had each been assigned as the lower field one of the pair. The lower field ^{1}H signal had been agreed as arising from H-4 (NOE with N-CH_3[17]) and so a $^{1}J_{CH}$ HETCOR experiment on **7i**

Table 1. ^{13}C Chemical Shifts for Acridinones in $CDCl_3$.[A]



	7a	**7b**[B]	**7c**	**7d**[C]	**7e**	**7f**[D]	**7g**	**7h**[D]	**7i**[B,C]	**7j**	**7k**[D]	**7l**	**7m**
1	168.1	161.8	162.7	167.7	162.7	161.7	168.3	*162.0*	*162.6*	*162.5*	164.0	169.1	163.0
2	107.2	105.7	103.8	107.1	105.4	105.5	107.9	104.7	*106.1*	103.9	104.2	107.7	104.7
3	139.2	135.9	135.7	139.2	135.6	135.2	138.1	134.4	135.9	135.9	135.6	138.8	135.4
4	102.7	106.1	106.6	103.3	107.2	107.1	101.8	106.6	*106.2*	108.1	107.3	102.8	107.8
4a	143.4	141.8	141.8	142.5	140.4	141.7	142.9	141.0	141.7	143.1	143.0	142.0	140.0
10a	139.9	140.9	142.8	131.4	131.5	131.7	144.2	145.2	143.5	145.0	144.8	133.3	133.3
5	117.6	117.4	115.0	147.7	146.6	145.9	94.6	93.1	91.3	90.0	91.1	141.1	139.7
6	134.6	134.5	134.3	112.4	111.9	114.9	*165.2*	*164.4*	*164.9*	*164.6*	*165.4*	113.1	112.6
7	122.8	121.7	121.0	122.1	121.0	121.4	91.1	90.3	96.4	94.6	96.7	101.5	100.5
8	126.0	125.3	125.7	116.6	117.2	116.2	*162.4*	*162.4*	*160.7*	*166.3*	*162.0*	153.9	154.2
8a	120.2	119.0	120.1	120.5	120.3	120.1	106.0	105.2	102.1	105.5	102.7	111.2	110.8
9	182.5	181.7	181.3	182.3	182.5	181.7	181.9	181.6	183.0	183.4	182.6	182.9	183.2
9a	108.6	108.5	109.1	108.7	109.5	108.7	109.0	109.5	106.8	107.6	107.6	109.5	110.3
CH_3CH_2	14.3	-	-	14.3	-	-	14.3	-	-	-	-	14.3	-
CH_3CH_2	61.0	-	-	61.0	-	-	61.0	-	-	-	-	60.9	-
C=O	168.9	-	-	168.9	-	-	169.3	-	-	-	-	167.5	-
CH_3O	-	-	-	56.3	56.0	-	55.7	55.3	-	55.5	-	56.2	56.2
CH_3O	-	-	-	-	-	-	56.3	56.0	-	-	-	56.5	56.2
NCH_3	-	-	33.9	-	-	-	-	-	-	34.6	34.6	-	-

[A] Assignments in italics are uncertain [B] DMSO-d_6 [C] CH from HETCOR [D] $CDCl_3$ + DMSO-d_6

showed that the lower field C signal was from C-2 (C-7 in Table 1). A similar disagreement was noted with respect to C-6 and C-8 in 5-oxy compounds.[18, 19] Again it had been established that H-8 gave rise to the lower field doublet[17,20] and so $^1J_{CH}$ HETCOR on **7d** established that C-8 gave the lower field signal.

The work presented here illustrates a versatile reaction applicable to the synthesis of multioxy substituted acridones. It is more general than our original report of the reaction of **3a** with diethyl ethoxymethylenemalonate.[21] It provides a useful alternative to the standard cyclization of diphenylamine-2-carboxylic acids,[22] as the precursors for some substitution patterns are more accessible. Further developments to give derivatives with potentially interesting and varied biological activity are possible.

EXPERIMENTAL

General. 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. Ortho coupling constants were typically ≈8 Hz and in these cases multiplicities alone are recorded. Ethyl esters had appropriate multiplets at ≈1.3 and 4.2 ppm. Proton-coupled carbon spectra were used to determine numbers of protons attached to the various carbons. The (^{13}C-^1H) HETCOR experiment was performed using the pulse sequence described by Bax and Morris.[23] The refocusing delay was optimized to 160 Hz (3.45 ms). The spectrum was acquired as 512 x 256 data points, zero filled and subjected to both Fourier transforms to afford the 1024 x 1024 point data matrix. The number of transients per t_1 increment was 256. Spectral widths were 2252 Hz in F_1 (^1H) and 19230 Hz in F_2 (^{13}C). The 90° pulse widths were 14.0 ms (^1H) and 13.5 ms (^{13}C). 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. EI mode high-resolution mass spectra were obtained by Dr N. Davies, University of Tasmania. Ir spectra were recorded on a Perkin-Elmer 1720X FTIR spectrometer, using a diffuse reflectance accessory with KBr background.

Preparation of compounds according to Scheme 1.

Each of the three steps was carried out by the procedure reported.[8] The formation of **5** was improved if the intermediate **4** was purified by column chromatography (silica/ethyl acetate). With the pairs **4b/8a** and **4d/8b**, separation was not complete. The heating time for the conversion of **4** to **5** is indicated in each case. A characteristic of **5** was the red colour in all cases of W=MeO. Microanalytical figures are reported for representatives of each of **3**, **4**, **5**, and **8**. Electrospray mass spectra, and NMR spectra indicative of homogeneous samples were the criteria used for analogues. The following new compounds were prepared in these ways:

Ethyl (1,4-Dihydro-8-methoxy-4-oxoquinolin-2-yl)acetate (3b). 86% (from *o*-methoxyaniline), m.p. 174-176 °C (from ethyl acetate). ^1H NMR δ 3.71 (s, CH_2), 3.97 (s, OMe), 6.20 (s), 7.00 (d), 7.22 (t), 7.85 (d). ^{13}C NMR δ 13.9 (Me), 38.0 (CH_2), 56.0 (OMe), 61.9 (OCH_2), 110.4 (CH), 110.5 (CH), 116.9 (CH), 123.1 (CH), 125.7 (C), 130.8 (C), 143.6 (C), 147.9 (C), 169.4 (CO), 178.4 (CO). ESMS: m/z 262 (M+1). Found: C, 64.5; H, 5.6; N, 5.5. Calcd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4%.

Ethyl (1,4-Dihydro-5,7-dimethoxy-4-oxoquinolin-2-yl)acetate (3c). 89% (from 3,5-dimethoxyaniline), m.p. 192-194 °C (from ethyl acetate). ^1H NMR δ 3.73 (s, CH_2), 3.78 (s, OMe), 3.86 (s, OMe), 6.31 (d, J=2.1 Hz), 6.34 (s), 6.70 (d, J=2.1 Hz). ^{13}C NMR δ 14.0 (Me), 40.9 (CH_2), 55.5 (OMe), 56.1

(OMe), 61.4 (OCH_2), 95.8 (CH), 96.4 (CH), 108.3 (C), 108.6 (CH), 147.9 (C), 149.7 (C), 158.9 (C), 162.0 (C), 169.8 (CO), 173.2 (CO). ESMS: m/z 292 (M+1).

Ethyl (1,4-Dihydro-5,8-dimethoxy-4-oxoquinolin-2-yl)acetate (3d). 71% (from 2,5-dimethoxyaniline), m.p. 146-148 °C (from ethyl acetate). ^1H NMR δ 3.63 (s, CH_2), 3.73 (s, OMe), 3.74 (s, OMe), 6.08 (s), 6.42 (d), 6.74 (d). ^{13}C NMR δ 13.7 (Me), 38.4 (CH_2), 55.8 (OMe), 56.1 (OMe), 61.4 (OCH_2), 102.9 (CH), 109.9 (CH), 111.7 (CH), 115.2 (C), 134.0 (C), 142.6 (C), 144.1 (C), 152.2 (C), 169.2 (CO), 176.1 (CO). ESMS: m/z 292 (M+1).

Diethyl 2-(1,4-Dihydro-8-methoxy-4-oxoquinolin-2-yl)pentandioate (4b). 42% as an oil, R_f 0.47. ^1H NMR δ 2.15-2.48 (m, 2xCH_2), 3.70 (t, J = 7 Hz, 1H), 3.93 (s, OMe), 6.14 (s), 6.96 (d), 7.16 (t), 7.79 (d). ^{13}C NMR δ 13.9 (Me), 14.0 (Me), 28.3 (CH_2), 31.2 (CH_2), 48.1 (CH), 56.0 (OMe), 60.7 (OCH_2), 62.1 (OCH_2), 110.0 (CH), 110.5 (CH), 117.0 (CH), 123.2 (CH), 125.8 (C), 130.7 (C), 146.9 (C), 147.9 (C), 171.9 (CO), 172.0 (CO), 178.4 (CO). ESMS: m/z 362 (M+1).

Diethyl 2-(1,4-Dihydro-8-methoxy-4-oxoquinolin-2-yl)-2-hydroxypentandioate (8a). 26 % as an oil, R_f 0.47. ^1H NMR δ 2.35-2.46 (m, 2xCH_2), 3.96 (s, OMe), 6.58 (s), 7.01 (d), 7.23 (t), 7.83 (d). ^{13}C NMR δ 13.9 (Me), 14.0 (Me), 28.7 (CH_2), 34.4 (CH_2), 56.0 (OMe), 60.8 (OCH_2), 64.0 (OCH_2), 75.8 (C), 107.2 (CH), 110.6 (CH), 118.9 (CH), 123.8 (CH), 125.7 (C), 129.8 (C), 148.1 (C), 148.5 (C), 171.6 (CO), 172.7 (CO), 178.8 (CO). ESMS: m/z 378 (M+1).

Diethyl 2-(1,4-Dihydro-5,7-dimethoxy-4-oxoquinolin-2-yl)pentandioate (4c). 92%, R_f 0.24, m.p. 165-166 °C (from ethyl acetate). ^1H NMR δ 2.20-2.40 (m, 2xCH2), 3.75 (t, J = 7 Hz, 1H), 3.79 (s, OMe), 3.87 (s, OMe), 6.32 (d, J = 1.3 Hz), 6.39 (s), 6.74 (d, J = 1.3 Hz). ^{13}C NMR δ 14.1 (2xMe), 27.2 (CH_2), 31.8 (CH_2), 51.0 (CH), 55.5 (OMe), 56.1 (OMe), 60.4 (OCH_2), 61.3 (OCH_2), 96.6 (CH), 97.0 (CH), 106.5 (CH), 107.9 (C), 148.8 (C), 154.8 (C), 158.5 (C), 161.6 (C), 169.4 (CO), 171.9 (CO), 172.6 (CO). ESMS: m/z 392 (M+1). Found: C, 61.5; H, 6.4; N, 3.5. Calcd for $C_{20}H_{25}NO_7$: C, 61.4; H, 6.4; N, 3.6%.

Diethyl 2-(1,4-Dihydro-5,8-dimethoxy-4-oxoquinolin-2-yl)pentandioate (4d). 33 %, R_f 0.15, m.p. 116-118 °C (from ethyl acetate). ^1H NMR δ 2.10-2.29 (m, 2xCH_2), 3.61 (t, J = 7.1 Hz, 1H), 3.82 (s, OMe), 3.87 (s, OMe), 6.13 (s), 6.50 (d), 6.84 (d).^{13}C NMR δ 13.8 (Me), 13.9 (Me), 27.9 (CH_2), 31.2 (CH_2), 48.4 (CH), 56.0 (OMe), 56.3 (OMe), 60.5 (OCH_2), 61.7 (OCH_2), 103.1 (CH), 108.9 (C), 110.2 (CH), 111.3 (CH), 133.9 (C), 142.5 (C), 147.0 (C), 152.5 (C), 171.9 (CO), 172.0 (CO). ESMS: m/z 392 (M+1).

Diethyl 2-(1,4-Dihydro-5,8-dimethoxy-4-oxoquinolin-2-yl)-2-hydroxypentandioate (8b). 9 %, R_f 0.15, m.p. 135-136 °C (from ethyl acetate). ^1H NMR δ 2.30-2.6 (m, 2xCH_2), 3.94 (s, OMe), 3.95 (s, OMe), 6.65 (d), 6.75 (s), 6.93 (d).^{13}C NMR δ 14.0 (Me), 14.1 (Me), 28.8 (CH_2), 34.3 (CH_2), 56.3 (OMe), 56.6 (OMe), 60.8 (OCH_2), 63.6 (OCH_2), 76.3 (C), 104.1 (CH), 107.5 (CH), 110.5 (CH), 172.2 (CO), 172.9 (CO)—incomplete, with other low intensity, broad signals in the range 110-150 ppm. ESMS: m/z 408 (M+1). IR 3380, 3020 (br), 1730, 1620 cm^{-1}. Found: C, 58.7; H, 6.5; N, 3.4. Calcd for $C_{20}H_{25}NO_8$: C, 59.0; H, 6.2; N, 3.4%.

Ethyl 1,9-Dioxo-1,2,3,4,9,10-hexahydro-5-methoxyacridine-4-carboxylate (5b). PPA 5 h, 88%, red, m.p. 169-170 °C (from ethyl acetate). ^1H NMR (DMSO-d_6) δ 2.27-2.50 (m, 2xCH_2),3.98 (s, OMe), 4.41 (br s, H-4), 7.31 (2xd), 7.67 (t), 11.58 (s, NH). ^{13}C NMR (DMSO-d_6) δ 14.1 (Me), 24.1 (CH_2), 35.5 (CH_2), 43.8 (CH), 56.5 (OMe), 61.5 (OCH_2), 112.7 (CH), 114.2 (C), 117.0 (CH), 124.6 (CH), 128.3 (C), 128.7 (C), 148.6 (C), 156.3 (C), 170.4 (CO), 173.7 (CO), 192.0 (CO). ESMS: m/z 316 (M+1). Found: C, 64.6; H, 5.3; N, 4.3. Calcd for $C_{17}H_{17}NO_5$: C, 64.8; H, 5.4; N, 4.4%.

1,2,3,4,9,10-Hexahydro-5-methoxyacridine-1,9-dione (5c). PPA 16h, 73%, off-white, m.p. 224-226 °C (from ethyl acetate/ethanol). ^{1}H NMR δ 2.19 (p, J = 6.3 Hz, H-3), 2.76 (t, J = 6.3 Hz, H-2), 3.26 (t, J = 6.3 Hz, H-4), 4.03 (s, OMe), 7.14 (d), 7.39 (t), 7.85 (d). ^{13}C NMR δ 21.5 (CH_2), 32.7 (CH_2), 38.3 (CH_2), 56.2 (OMe), 109.9 (C), 112.1 (CH), 115.6 (CH), 121.6 (C), 125.9 (CH), 138.9 (C), 153.3 (C), 161.5 (C), 169.7 (CO), 204.3 (CO). ESMS: m/z 244 (M+1)

Ethyl 6,8-Dimethoxy-1,9-dioxo-1,2,3,4,9,10-hexahydroacridine-4-carboxylate (5d). PPA 6 h, 84%, orange, m.p. 109-112 °C (from ethyl acetate). ^{1}H NMR δ 2.40-3.02 (m, H-2,3), 3.90 (s, OMe), 3.95 (s, OMe), 4.05 (t, J = 7.1 Hz, H-4), 6.43 (d, J = 2.4 Hz), 6.87 (d, J = 2.4 Hz). ^{13}C NMR δ 14.1 (Me), 24.6 (CH_2), 34.8 (CH_2), 48.3 (CH), 55.8 (OMe), 56.1 (OMe), 61.2 (OCH_2), 98.2 (CH), 101.3 (CH), 106.1 (C), 107.8 (C), 153.9 (C), 159.7 (C), 160.1 (C), 164.4 (C), 170.4 (CO), 171.6 (CO), 203.5 (CO). ESMS: 345 (M+1).

6,8-Dimethoxy-1,2,3,4,9,10-hexahydroacridine-1,9-dione (5e). PPA 20 h, 70%, yellow, m.p. 105-107 °C (from ethyl acetate). ^{1}H NMR δ 2.15 (p, J = 6.3 Hz, H-3), 2.72 (t, J = 6.3 Hz, H-2), 3.05 (t, J = 6.3 Hz, H-4), 3.89 (s, OMe), 3.94 (s, OMe), 6.40 (d, J = 1.9 Hz), 6.85 (d, J = 1.9 Hz). ^{13}C NMR δ 21.5 (CH_2), 33.0 (CH_2), 38.0 (CH_2), 55.7 (OMe), 56.2 (OMe), 97.9 (CH), 100.4 (CH), 106.0 (C), 108.2 (C), 153.9 (C), 160.3 (C), 163.7 (C), 164.6 (C), 170.6 (CO), 204.7 (CO). ESMS: m/z 274 (M+1)

Ethyl 5,8-Dimethoxy-1,9-dioxo-1,2,3,4,9,10-hexahydroacridine-4-carboxylate (5f). PPA 6 h, 60%, red, m.p. 119-122 °C (from ethyl acetate), still slightly impure. ^{1}H NMR δ 2.55-2.7 (m, 2xCH_2), 3.85 (s, OMe), 3.90 (s, OMe), 3.93 (t, J = 5.1 Hz, H-4), 6.32 (d), 6.86 (d). ESMS: 346 (M+1).

2-(2-Oxo-2,3,4,5-tetrahydrofuran-5-yl)-8-methoxyquinolin-4(1H)one (9a). PPA 16 h, 70 %, m.p. 242-243 °C (from ethyl acetate). ^{1}H NMR δ 2.3-2.42 (m, 1H), 2.65-2.85 (m, 3H), 4.00 (s, OMe), 5.60 (t, J = 7.7 Hz, 1H), 6.29 (s), 7.09 (d), 7.28 (t), 7.85 (d).^{13}C NMR δ 28.2 (CH_2), 28.9 (CH_2), 56.0 (OMe), 76.4 (CH), 106.1 (CH), 110.9 (CH), 117.1 (CH), 124.0 (CH), 128.0 (C), 130.2 (C), 147.9 (C), 148.0 (C), 175.0 (CO), 178.1 (CO). ESMS: m/z 260 (M+1).

2-(2-Oxo-2,3,4,5-tetrahydrofuran-5-yl)-5,8-dimethoxyquinolin-4(1H)one (9b). PPA 16 h, 67 %, m.p. 100-102 °C (from ethyl acetate). ^{1}H NMR δ 2.3-2.45 (m, 1H), 2.6-2.85 (m, 3H), 3.95 (s, OMe), 3.96 (s, OMe), 5.83 (t, J = 7.5 Hz, 1H), 6.67 (d), 6.69 (s), 6.89 (d).^{13}C NMR δ 28.2 (CH_2), 28.9 (CH_2), 56.2 (OMe), 56.4 (OMe), 80.0 (CH), 103.6 (CH), 104.9 (CH), 108.7 (CH), 176.4 (CO)—incomplete, aromatic quaternary C very low intensity. ESMS: m/z 290 (M+1). Found: EIMS $(M-H)^+$, 288.08725. $C_{15}H_{14}NO_5$ requires 288.08724.

Aromatization.

Method A. To a solution of **5a** (0.6 mmol) in acetic acid (20 ml) was added dropwise, a solution of bromine in acetic acid (0.2 M, 3 ml, 0.6 mmol). A green colour developed immediately. As soon as addition was complete, water (50 ml) was added and the mixture was extracted with chloroform (3 x 20 ml). The extracts were washed with saturated sodium bicarbonate solution, water, 10% sodium metabisulfite solution, water, dried, and the solvent was removed at reduced pressure. The residue was dissolved in ethanol (15 ml), dimethylaniline (0.5 ml) was added and the mixture was refluxed under nitrogen for 2 h. The solution was concentrated to a small volume and cooled, and the product, **7a**, separated

Method B. A mixture of **5** and one third of its weight of 10% palladium on charcoal in diphenyl ether (20 ml/g of **5**) was heated under reflux, with stirring, for 30 min. (retention of ester group) or 3 h (loss of ester).

After removal of the catalyst, light petroleum (b.p. 60-90 °C) was added to the cooled mixture, and the product **7** was filtered off, dried, and recrystallized. This method was used for all **7** reported below.

Demethylation.

A mixture of a methoxyacridone (with or without an ester function—this was lost during the reaction) (0.1 g) and 40% hydrobromic acid (10 ml) was stirred and refluxed for 7 h (16 h needed for **7g/7h**) then cooled and water (40 ml) was added. The mixture was stirred for 4 h at room temperature and the product was filtered off and recrystallized from ethanol/water.

Methylation.

A mixture of the acridone (0.03 g), anhydrous potassium carbonate (0.09 g) and methyl iodide (0.2 g) in dry acetone (3 ml) was refluxed for 3 h. The mixture was filtered and the filtrate evaporated under reduced pressure.

By these methods, as appropriate, the following yellow compounds were prepared (^{13}C NMR data are collected in Table 1):

Ethyl 1-Hydroxy-9-oxo-9,10-dihydroacridine-4-carboxylate (7a). 88%, m.p. 153-154 °C (from ethanol). ^1H NMR δ 6.61 (d), 7.33 (t), 7.41 (d), 7.72 (t), 8.31 (d), 8.38 (d), 12.32 (br s, NH), 15.12 (br s, OH). ESMS: m/z 284 (M+1). Found: C, 67.6, H, 4.5, N, 4.9. Calcd for $C_{16}H_{13}NO_4$: C, 67.8; H, 4.6; N, 4.9.

1-Hydroxy-9(10H)-acridinone (7b). 54%, m.p. 250-252 °C (lit.[11] m.p. 252-254 °C). ^1H NMR (DMSO-d_6) δ 6.52 (d), 6.93 (d), 7.29 (d-d), 7.54-7.59 (m, 2H), 7.75 (t), 8.19 (d), 12.13 (s, NH), 13.98 (s, OH). ESMS: m/z 212 (M+1).

1-Hydroxy-10-methyl-9(10H)-acridinone (7c). 94%, m.p. 192-194 °C (lit.[11] m.p. 195-196 °C). ^1H NMR δ 3.26 (s, NMe), 5.97 (d), 6.36 (d), 6.67 (t), 6.96 (t), 7.04 (d), 7.16 (t), 7.72 (d), 13.81 (s, OH). ESMS: m/z 226 (M+1).

Ethyl 1-Hydroxy-5-methoxy-9-oxo-9,10-dihydroacridine-4-carboxylate (7d). 90%, m.p. 173-174 °C (from ethanol). ^1H NMR δ 4.08 (s, OMe), 6.61 (d), 7.14 (d), 7.24 (t), 7.91 (d), 8.30 (d), 12.48 (br s, NH). ESMS: m/z 314 (M+1). Found: C, 65.5; H, 5.0; N, 4.6. Calcd for $C_{17}H_{15}NO_5$: C, 65.2; H, 4.8; N, 4.5%.

1-Hydroxy-5-methoxy-9(10H)-acridinone (7e). 91%, m.p. 218-220 °C (from ethanol). ^1H NMR d 3.99 (s, OMe), 6.61 (d), 6.72 (d), 7.03 (d), 7.11 (t), 7.46 (t), 7.86 (d), 8.68 (br s, NH), 13.89 (br s, OH). ESMS: m/z 242 (M+1).

1,5-Dihydroxy-9(10H)-acridinone (7f). 83%, m.p. >300 °C (from ethanol/water). ^1H NMR ($CDCl_3$+DMSO-d_6) δ 6.46 (d), 7.09 (t), 7.18 (d), 7.32 (d), 7.50 (t), 7.65 (d), 10.80 (s, NH(OH)), 11.47 (s, OH(NH)), 14.08 (s, OH). ESMS: m/z 228 (M+1).

Ethyl 6,8-Dimethoxy-1-hydroxy-9-oxo-9,10-dihydroacridine-4-carboxylate (7g). 77%, m.p. 230-232 °C (from ethanol). ^1H NMR δ 3.89 (s, OMe), 3.98 (s, OMe), 6.25 (d, J = 1.7 Hz), 6.30 (d, J = 1.7 Hz), 6.55 (d), 8.20 (d), 12.14 (s, NH), 15.77 (br s, OH). ESMS: m/z 344 (M+1). Found: C, 62.7; H, 5.3; N, 3.8. Calcd for $C_{18}H_{17}NO_6$: C,63.0; H, 5.0; N, 4.1%.

1,3-Dimethoxy-8-hydroxy-9(10H)-acridinone (7h). 84%, m.p. 233-235 °C (from chloroform). ^1H NMR ($CDCl_3$+DMSO-d_6) δ 3.71 (s, OMe), 3.78 (s, OMe), 6.01 (d, J = 1.9 Hz), 6.28 (d, J = 1.9 Hz), 6.32 (d), 6.58 (d), 7.21 (t), 10.96 (br s, NH). ESMS: m/z 272 (M+1).

1,3,8-Trihydroxy-9(10H)-acridinone (7i). 84% from **7g**, m.p. >300 °C (dec) (from ethanol/water). ^{1}H NMR (DMSO-d_6) δ 6.03 (s), 6.30 (s), 6.49 (d), 6.84 (d), 7.53 (t), 10.71 (s, NH(OH)), 11.93 (s, OH(NH)), 12.73 (s, OH), 12.76 (OH). ESMS: m/z 244 (M+1). Found: C, 64.1; H, 3.5; N, 5.6. Calcd for $C_{13}H_9NO_4$: C, 64.2; H, 3.7; N, 5.8%.

1,8-Dihydroxy-3-methoxy-10-methyl-9(10H)-acridinone (7j). ^{1}H NMR δ 3.63 (s, NMe), 3.84 (s, OMe), 6.14 (d, J = 1.7 Hz), 6.17 (d, J = 1.7 Hz), 6.58 (d), 6.74 (d), 7.47 (t), 13.26 (s, OH), 13.43 (s, OH). ESMS: m/z 272 (M+1).

This compound was not purified but was further characterized by demethylation to **7k**.

10-Methyl-1,3,8-trihydroxy-9(10H)-acridinone (7k). 88% from **7i**, m.p. 285-288 °C (lit.[11] m.p. 285-290 °C). ^{1}H NMR (DMSO-d_6) δ 3.67 (s, NMe), 6.08 (d, J = 1.6 Hz), 6.30 (d, J = 1.6 Hz), 6.51 (d), 6.88 (d), 7.50 (t), 10.4 (v br s, OH), 13.25 (br s, 2xOH). ESMS: m/z 258 (M+1).

Ethyl 5,8-Dimethoxy-1-hydroxy-9-oxo-9,10-dihydroacridine-4-carboxylate (7l). 59%, m.p.196-199 °C. ^{1}H NMR δ 3.98 (s, OMe), 4.04 (s, OMe), 6.56-6.61 (m, 2H), 7.07 (d), 8.28 (d), 12.47 (s, NH), 13.95 (s, OH). ESMS: m/z 344 (M+1).

1,4-Dimethoxy-8-hydroxy-9(10H)-acridinone (7m). 59%, m.p.166-169 °C.
^{1}H NMR δ 3.95 (s, OMe), 3.97 (s, OMe), 6.49 (d), 6.60 (d), 6.68 (d), 6.99 (d), 7.45 (t), 8.66 (br s, NH). ESMS: m/z 272 (M+1). Found: EIMS (M^+), 271.08520. $C_{15}H_{13}NO_4$ requires 271.08450.

Single-crystal X-ray structure determination of 8b.

The crystal data and refinement are summarized in Table 2.

Table 2. Crystal Refinement Data for Compound **8b**.[24]

Empirical formula	$C_{20}H_{28}NO_8$	Data measured	5186
Formula weight	410.5	*h,k,l* range	*h* -15 to 15
			k -14 to 14
			l 0 to 15
Crystal system	monoclinic	Unique data	2593
Space group	*C* 2/*c*	Observed reflect.	1105(I>4σI)
Cell dimensions	*a* 18.542(4) Å	Decay	<1.5%
	b 14.426(3) Å	R(int)	0.037
	c 18.338(4) Å	Data/parameters	1105/118
	β 123.04(2)°	$R = \Sigma\|\Delta F\|/\Sigma\|F_o\|$	0.106
V	4140(4) Å^3	Max. shift/error	0.04
Z	8	Mean shift/error	0.005
Density (calc.)	1.304 g cm^{-3}	Max.diff.peak	0.35 e Å^{-3}
F(000)	1720	Min.diff.peak	0.32 e Å^{-3}
		μ(Cu Kα)	8.13 cm^{-1}

Intensity data were measured at 292(2) K from a colourless tabular crystal of approximate dimensions 0.035 x 0.108 x 0.04 mm. The cell dimensions were refined by a least-squares fit of θ values for 25 reflections

within the range 17-29°. The data were recorded on a Rigaku-AFC diffractometer with Cu Kα radiation (graphite-crystal monochromator, λ =1.5418 Å) using a 2θ/ω scan. Due to the poor crystal quality, the data were only measured to a $2\theta_{max}$ of 100°. The measured intensities were corrected for Lorentz and polarization effects and for absorption (transmission factors 0.750-0.935). The structure was solved by direct methods with SHELX86[25] and refined with SHELX76.[26] In the refinement, the bond lengths within the ethoxycarbonyl moieties were constrained to within 0.005 Å of their expected values, as disorder was evident in the two ester groups and for which no suitable disorder model could be found. The structure was refined with 1105 terms for which $I > 4\sigma I$ and with unit weights. Due to the limited number of data terms, the non-hydrogen atoms were given isotropic temperature factors whereas the hydrogen atoms (apart from that of the hydroxyl which was not located) were included at idealised positions and given a common isotropic temperature factor (B = 18.0(15) Å^2). Atomic scattering factors were taken from International Tables for X-ray Crystallography.[27]

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