Natural Products Chemistry. Part 124.[1] Revised Structure and Synthesis of a New Acridone Alkaloid, Hallacridone from *Ruta graveolens* Tissue Cultures[2]

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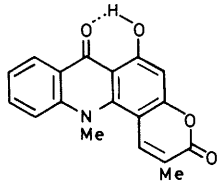
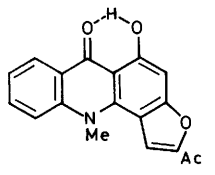
The synthesis of 6-hydroxy-2,12-dimethyl-3*H*-pyrano[2,3-*c*]acridine-3,7(12*H*)-dione (**1**) by two different routes revealed the previously proposed structure of hallacridone, to be incorrect. Careful examination of the spectral characteristics, of an authentic sample of hallacridone, led us to suggest a revised structure, 2-acetyl-5-hydroxy-11-methylfuro[2,3-*c*]acridin-6(11*H*)-one (**2**), which we unambiguously confirmed by total synthesis. The biosynthetic significance of hallacridone (**2**) is discussed.

Hallacridone is a minor acridone alkaloid isolated from tissue cultures of *Ruta graveolens* and structure (**1**) was assigned to it on the basis of spectroscopic evidence.[2] Prompted by its unique 3-methylcoumarino structure and in our continuing studies on Rutaceae alkaloids we undertook the synthesis of (**1**) in order to confirm this assignment.



(1)



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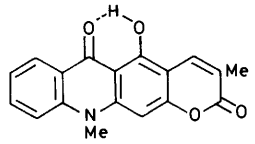

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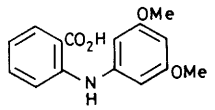

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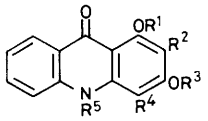
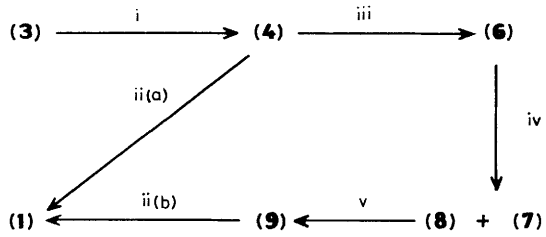


(3) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Me$
(4) $R^1 = R^2 = R^4 = H$, $R^3 = CH_2C(=CH_2)CO_2Et$, $R^5 = Me$
(6) $R^1 = R^4 = H$, $R^2 = I$, $R^3 = CH_2C(=CH_2)CO_2Et$, $R^5 = Me$
(7) $R^1 = R^3 = Ac$, $R^2 = I$, $R^4 = CH_2C(=CH_2)CO_2Et$, $R^5 = Me$
(8) $R^1 = R^3 = Ac$, $R^2 = H$, $R^4 = CH_2C(=CH_2)CO_2Et$, $R^5 = Me$
(9) $R^1 = R^2 = R^3 = H$, $R^4 = CH_2C(=CH_2)CO_2H$, $R^5 = Me$
(13) $R^1 = R^3 = Me$, $R^2 = R^5 = H$, $R^4 = CHO$
(14) $R^1 = R^3 = R^5 = Me$, $R^2 = H$, $R^4 = CHO$
(15) $R^1 = R^2 = H$, $R^3 = R^5 = Me$, $R^4 = CHO$
(16) $R^1 = R^2 = R^3 = H$, $R^4 = CHO$, $R^5 = Me$

1,3-Dihydroxy-10-methylacridin-9(10*H*)-one (**3**) and ethyl bromomethacrylate were treated to give compound (**4**), which on heating in PEG 200[3] underwent the following: *ortho*-Claisen rearrangement and ring closure followed by double-bond isomerisation (see Scheme 1). Although the ^1H n.m.r. and i.r. spectra of the product thus obtained showed the appropriate characteristics for an acridone alkaloid containing a 3-methylcoumarin ring system (see Experimental section), they were not consistent with those reported for hallacridone.[2] Because the *ortho*-Claisen rearrangement might occur towards either C-4 or C-2 of the acridone nucleus, the possibility arose that it was in fact the linear isomer (**5**). Further, at this point, the doublet nature of the coumarin CH_3 signal (δ 2.22 d, J 1.4 Hz) in the ^1H n.m.r. spectrum of our synthetic sample and the absence of such a doublet in that of hallacridone led us to doubt the previously proposed structure. The poor solubility of the synthetic compound in almost all solvents prevented us in carrying out an n.O.e. experiment (irradiating at the N–Me signal) which would have resolved this problem. Therefore we decided to protect the C-2 of the acridone nucleus of compound (**4**) and then carry out the Claisen rearrangement in order to obtain (1).

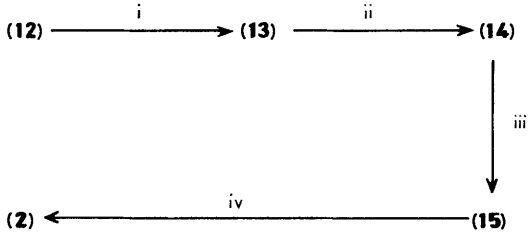
It has been reported,[4] that iodination of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one (**3**), and its mono- or di-methyl ethers, with I_2/HIO_4 in aqueous ethanol occurs at C-2 of the acridone nucleus. Compound (**4**) was successfully iodinated by this method to give ethyl 2-(1′-hydroxy-2′-iodo-9′-oxo-9′,10′-dihydroacridin-3′-yloxymethyl)propenoate (**6**). Treatment of compound (**6**) with pyridine and acetic anhydride at 100 °C yielded a complex mixture of products, from which ethyl 2-(1′,3′-diacetoxy-2′-iodo-9′-oxo-9′,10′-dihydroacridin-4′-ylmethyl)propenoate (**7**) and ethyl 2-(1′,3′-diacetoxy-9′-oxo-9′,10′-dihydroacridin-4′-ylmethyl)propenoate (**8**) were isolated. The observation that (**7**) underwent slow decomposition to produce (**8**) in chloroform solution indicated that the side chain was situated at C-4 of the acridone nucleus. This was confirmed by carrying out an n.O.e. experiment on the acridone (**8**); the n.O.e. difference spectrum at 300 MHz, showed unambiguous enhancements for 5-H, benzylic CH_2, and one of the vinylic proton signals, upon irradiation of the N–Me signal at δ 3.74 of the acridone derivative (**8**). Ester hydrolysis and deacetylation of compound (**8**) was effected with K_2CO_3 in methanol under reflux to yield the dihydroxy acid derivative (**9**). This, when heated in PEG 200, underwent simultaneous[3] cyclisation and double bond isomerisation to produce the desired 3-methylpyranoacridone (**1**) (see Scheme 1). This was found to be identical with the product obtained previously, by the direct Claisen rearrangement of (**4**) and was not comparable with hallacridone (by m.p., mixed m.p., t.l.c., i.r., ^1H n.m.r., and mass spectra). Hence the necessity to revise the structure of hallacridone was established.

The 300 MHz ^1H n.m.r. spectrum obtained for authentic hallacridone showed two sharp singlets at δ 7.93 for 1 H and δ 2.63 for 3 H, which had been assigned to protons of the 3-methylcoumarin ring system.[2] However, these two signals show none of the expected and mutual long-range coupling we expected for such a coumarin system.[5] Instead the 3 H singlet at δ 2.63 can be attributed more logically to a $COCH_3$ group of a 2-acetyl-

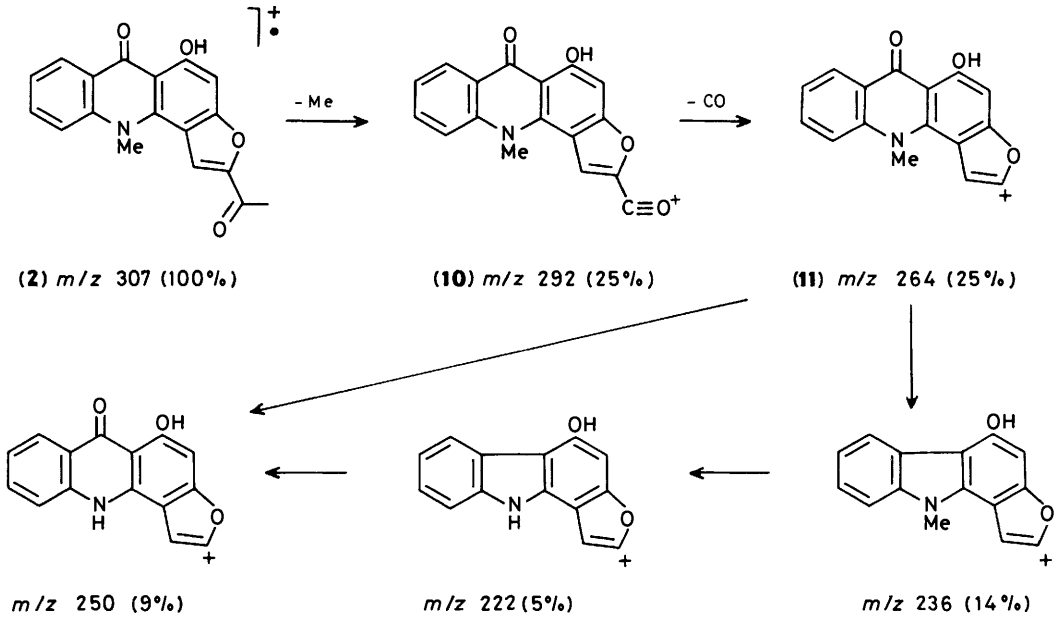


Scheme 1. *Reagents and conditions:* i, $BrCH_2C(=CH_2)CO_2Et$, anh. K_2CO_3, dry acetone reflux, 2 h; ii, PEG 200, 220 °C, (a) 0.5 h; (b) 15 min; iii, I_2, HIO_4, aq. ethanol, room temp., 2 h; iv, pyridine, Ac_2O, 100 °C, 3 h; v, K_2CO_3, MeOH, reflux 15 min

benzofuran ring system.[6] Further evidence for the presence of the $COCH_3$ group was provided by the i.r. spectrum which showed strong carbonyl absorption band at 1 670 cm^{-1} (αβ-unsaturated carbonyl group) and the mass spectrum which showed loss of Me (**10**) (*m/z* 292, $M^+ - 15$) followed by loss of CO (**11**) (*m/z* 264, $M^+ - 43$) (see Scheme 2). From this analysis extended to 72 h with an excess of reagent. Subsequent condensation of (**16**) with monochloroacetone in the presence of potassium carbonate in anhydrous acetone[10] yielded the desired 2-acetyl-5-hydroxy-11-methylfuro[2,3-*c*]acridin-6-(11*H*)-one (**2**), identical with authentic hallacridone (by m.p., mixed m.p., i.r., ^1H n.m.r., and t.l.c.) (see Scheme 3).



Scheme 3. *Reagents and conditions:* i, dry DMF, $POCl_3$, room temp., 1.5 h; ii, MeI, Ag_2O, dry DMF, room temp., 16 h; iii, BCl_3, dry CH_2Cl_2, room temp., 72 h; iv, $ClCH_2COCH_3$, anh. K_2CO_3, dry acetone, reflux, 2 h



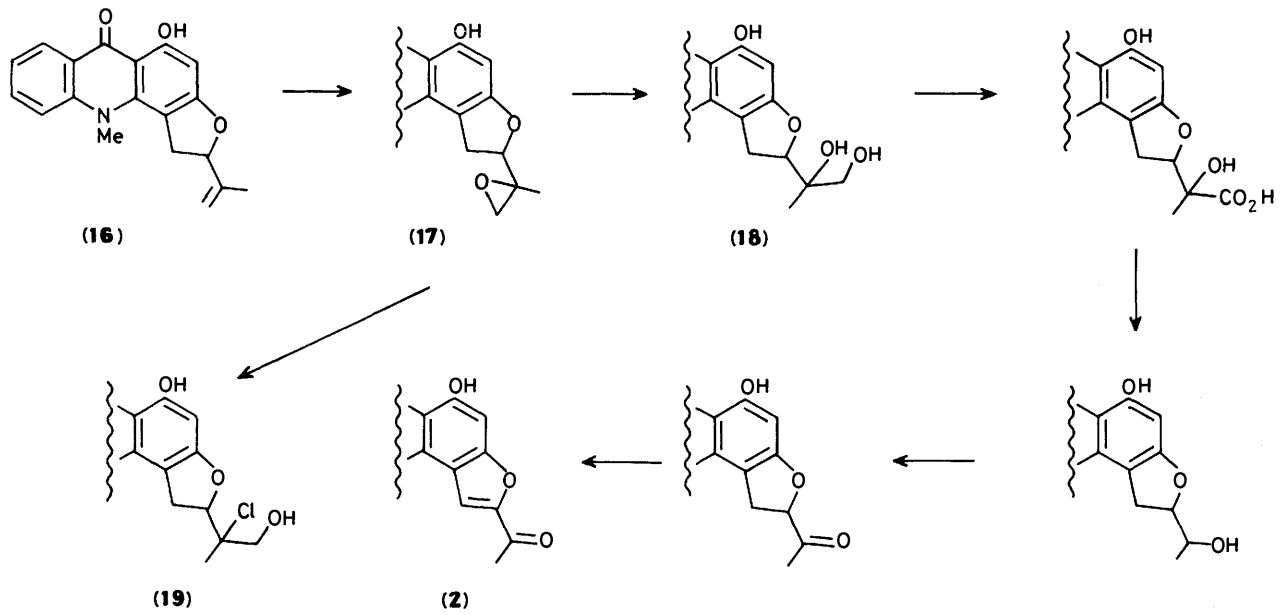
Scheme 2. Mass spectral fragmentation of hallacridone (**2**)

of the spectral data we arrived at the structure of hallacridone as 2-acetyl-5-hydroxy-11-methylfuro[2,3-*c*]acridin-6-(11*H*)-one (**2**). This result was unambiguously confirmed by a total synthesis of the compound. Thus the product (**12**), obtained by condensation of *o*-chlorobenzoic acid and 3,5-α-methoxyaniline under Ullman conditions, upon treatment with $DMF/POCl_3$ underwent simultaneous formylation[7] and cyclisation to yield 4-formyl-1,3-dimethoxyacridin-9(10*H*)-one (**13**). The position of the formyl group was confirmed by an n.O.e experiment after the *N*-methylation of compound (**13**) with MeI/Ag_2O in DMF.[8] The n.O.e difference spectrum at 300 MHz showed enhancements for 5-H and CHO signals upon irradiation at the N–Me protons at δ 3.65 of 4-formyl-1,3-dimethoxy-10-methylacridin-9(10*H*)-one (**14**). Demethylation of the formyldimethoxyacridone (**14**) with boron trichloride in CH_2Cl_2[9] over a period of 15 min gave exclusively the monomethoxy compound (**15**)* while complete demethylation, to yield the dihydroxy compound (**16**), was achieved only when the reaction time was

Biogenetic aspects.—*Ruta graveolens* has been subjected to extensive chemical investigation and the presence of several furoacridones including rutacridone (**16**), rutacridone epoxide (**17**), gravacridondiol (**18**) and some of their glucosides have been reported.[11–17] A detailed biosynthetic pathway has been proposed for the origin of these furoacridones implicating rutacridone (**16**) as precursor.[16]

As rutacridone (**16**), rutacridone epoxide (**17**), gravacridone-chlorine (**19**), and hallacridone (**2**) all occur in the same extract of *Ruta graveolens* tissue cultures[2] a biosynthetic relationship may exist between them as shown in Scheme 4. Although gravacridondiol (**18**) has not been detected in these particular

* The position of the methoxy group was established by the comparison of chemical shift values of CHO, NCH_3, and OH signals of compound (**15**) with those of dimethoxy- and dihydroxy-formyl acridones (**14**) and (**16**) (see Experimental section).



Scheme 4. Possible biosynthetic relationship between hallacridone (2) and some furoacridones isolated from roots and tissue cultures of *Ruta graveolens L*

extracts of tissue cultures,[2] it has been previously isolated from another extract of *Ruta graveolens* tissue culture.[16]

Experimental

General Procedures.—M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. I.r. spectra were recorded for KBr discs with a Pye Unicam SP 3-200 spectrophotometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ at 60 MHz or 300 MHz with $SiMe_4$ as internal reference on a Varian 60 A or Bruker WM 300 spectrometer. Mass spectra were obtained on a Varian MAT 44S instrument at 70 eV. Silica-gel 60 F_{254} (pre-coated aluminium sheets; 0.2 mm thickness; Merck 5549) were used for analytical t.l.c. whilst for preparative work silica-gel 60 F_{254} (pre-coated glass plates 2 mm thickness; Merck 5717 and 0.25 mm thickness; Merck 5715) were employed. Light petroleum had b.p. 30—40 °C. Bromomethacrylic acid was obtained from Aldrich Chemical Co.

Ethyl Bromomethacrylate.—Bromomethacrylic acid was esterified with ethanol in the presence of Me_3SiCl at 50 °C,[18] to yield ethyl bromomethacrylate as a colourless liquid; δ(60 MHz) 6.26, 5.90 (1 H each, br s, $=CH_2$), 4.25 (2 H, q, *J* 7 Hz, OCH_2Me), 4.18 (2 H, s, $BrCH_2$), and 1.33 (3 H, t, *J* 7 Hz, CH_2Me).

Preparation of Ethyl 2-(1′-Hydroxy-10′-methyl-9′-oxo-9′,10′-dihydroacridin-3′-yloxymethyl)propenoate (**4**).—Ethyl bromomethacrylate (0.75 g) and anhydrous K_2CO_3 (1.3 g) were added to a solution of 1,3-dihydroxy-10-methylacridin-9(10*H*)-one (**3**) (0.625 g) in dry acetone (250 ml) and the mixture was heated under reflux for 2 h. It was then filtered and the solids were washed with dichloromethane. The combined filtrates were evaporated to dryness to give a yellow solid which on recrystallisation from $CHCl_3$–MeOH yielded (**4**) as yellow needles (0.670 g, 73%), m.p. 139—140 °C (Found: C, 67.85; H, 5.35; N, 4.0. $C_{20}H_{19}NO_5$ requires C, 67.96; H, 5.42; N, 3.96%); $\nu_{max.}$ 3 660—3 250br, 2 980, 1 720, 1 640, 1 595, 1 550, 1 500, 1 470, 1 410, 1 400, 1 380, 1 335, 1 280, 1 235, 1 175, 1 150, 1 085, 1 030, 980, 920, 830, and 755 cm^{-1}; δ(60 MHz) 14.76 (1 H, s, OH), 8.35 (1 H, dd, *J* 8 and 2 Hz, 8-H), 7.83—7.06 (3 H, m, ArH), 6.46 (1 H, br s, =CH), 6.25 (2 H, br s, 2- and 4-H), 6.05 (1 H, br s, =CH), 4.81 (2 H, br s, OCH_2), 4.31 (2 H, q, *J* 7 Hz), 3.73 (3 H, s, NMe), and 1.36 (3 H, t, *J* 7 Hz, OCH_2Me); *m/z* 353 (M^+, 11%), 308 (6), 280 (100), 254 (8), 212 (39), 197 (8), 184 (6), 169 (6), 154 (8), 140 (6), 128 (5), 115 (6), and 85 (6).

Conversion of the Acridone (**4**) *into the 3-Methylpyranoacridone* (**1**).—The acridone (**4**) (0.080 g) was heated with polyethylene glycol (PEG 200) (15 ml) at 220 °C for 0.5 h with stirring.[3] The reaction mixture was poured into cold water and extracted with ether. The extract was washed with brine, dried (Na_2SO_4), and evaporated to dryness. Purification of the product by column chomatography on silica gel under medium pressure (eluant: 2% MeOH in CH_2Cl_2) and recrystallisation from toluene yielded (**1**) (0.038 g, 55%) as golden yellow needles, m.p. >328 °C (decomp.) (Found: C, 69.9; H, 4.3; N, 4.5. $C_{18}H_{13}NO_4$ requires C, 70.34; H, 4.26; N, 4.56%); $\nu_{max.}$ 3 620—3 300, 1 720, 1 625, 1 605, 1 565, 1 495, 1 460, 1 335, 1 305, 1 270, 1 220, 1 170, 1 150, 1 105, 1 065, 1 040, 922, 912, 820, 770, 760, 748, and 700 cm^{-1}; δ(300 MHz) 15.81 (1 H, s, OH), 8.50 (1 H, dd, *J* 1.8 and 7.8 Hz, 8-H), 7.97 (1 H, br s, 1-H), 7.81 (1 H, ddd, *J* 8.7, 6.9, and 1.8 Hz, 10-H), 7.57 (1 H, br d, *J* 8.8 Hz, 11-H), 7.38 (1 H, br t, *J* 7.8 Hz, 9-H), 6.73 (1 H, s, 5-H), 3.85 (3 H, s, NMe), and 2.19 (3 H, d, *J* 1.4 Hz, 2-*Me*); *m/z* 307 (M^+, 100%), 279 (61), 264 (40), 250 (18), 236 (10), 222 (16), 208 (6), 179 (10), 154 (14), 140 (15), 126 (16), 112 (8), 104 (8), 89 (13), and 77 (30).

Iodination of the Acridone (**4**).—The acridone (**4**) (0.502 g) in ethanol (75 ml) was iodinated with a solution of iodine (0.305 g) and periodic acid (0.060 g) in 85% ethanol (40 ml) at room temperature for 2 h. A solid separated and this was collected, washed with water, dried at the pump, and recrystallised from chloroform–methanol to give the iodoacridone (**6**) as pale yellow needles (0.610 g, 90%), m.p. 195—196 °C (Found: C, 50.15; H, 3.8; I, 26.5; N, 2.95. $C_{20}H_{18}INO_5$ requires C, 50.10; H, 3.78; I, 26.49; N, 2.92%); $\nu_{max.}$ 3 660—3 640, 3 000, 2 940, 1 720, 1 635, 1 595, 1 550, 1 480, 1 440, 1 390, 1 310, 1 272, 1 240, 1 180, 1 110, 1 090, 1 028, 940, 810, 780, 760, 710, and 660 cm^{-1}; δ(300 MHz), 15.90 (1 H, s, OH), 8.37 (1 H, dd, *J* 8 and 1.6 Hz, 8-H),

7.73 (1 H, ddd, *J* 8.6, 7.4, and 1.6 Hz, 6-H), 7.52 (1 H, br d, *J* 8.6, 5-H), 7.27 (1 H, br t, *J* 7.4, 7-H), 6.52, 6.41 (1 H each, br s, $=CH_2$), 6.27 (1 H, s, 4-H), 4.91 (2 H, s, OCH_2), 4.32 (2 H, q, *J* 7 Hz, OCH_2Me), 3.83 (3 H, s, N*Me*), and 1.38 (3 H, t, *J* 7 Hz, OCH_2Me); *m/z* 479 (M^+, 32%), 434 (4), 406 (10), 380 (10), 367 (20), 352 (74), 338 (10), 324 (43), 306 (41), 279 (100), 250 (30), 211 (30), 183 (49), 171 (74), 163 (46), 154 (30), 140 (24), 128 (47), 102 (13), and 77 (43).

Claisen Rearrangement of the Iodoacridone (**6**).—The iodoacridone derivative (**6**) (0.50 g) dissolved in pyridine (5 ml) was treated with acetic anhydride (2 ml) at 100 °C for 3 h. The solid, obtained on removal of solvents under reduced pressure, was chromatographed on silica (eluant: 1% MeOH in CH_2Cl_2) to yield the rearranged diacetoxyacridones (**7**) as a crystalline yellow solid (0.040 g, 7%) and (**8**) as pale green-yellow crystals (0.148 g, 32%).

Ethyl 2-(1′,3′-O-*diacetyl*-2′-*iodo*-9′-*oxo*-9′,10′-*dihydroacridin*-4′-*ylmethyl*)*propenoate* (**7**). M.p. 144—145 °C (Found: M^+, 563.0438. $C_{24}H_{22}INO_7$ requires *M*, 563.0439); $\nu_{max.}$ 2 940, 1 780, 1 720, 1 635, 1 610, 1 570, 1 490, 1 365, 1 255, 1 185, 1 095, 725, 860, 760, and 700 cm^{-1}; δ (60 MHz) 8.23 (1 H, dd, *J* 8 and 2 Hz, 8-H), 7.83—7.03 (3 H, m, ArH), 6.33, 5.46 (1 H each, br s, $=CH_2$), 4.30 (2 H, q, *J* 7 Hz, OCH_2Me), 3.83 (2 H, br s, $ArCH_2$), 3.73 (3 H, s, NMe), 2.56, 2.33 (3 H each, s, 2 × OCOMe), and 1.33 (3 H, t, *J* 7 Hz, CH_2Me); *m/z* 563 (M^+, 12%), 521 (100), 479 (57), 434 (22), 406 (44), 378 (26), 366 (22), 352 (36), 324 (40), 278 (52), 250 (48), 235 (20), 222 (23), 196 (28), 167 (28), 152 (25), 140 (25), 127 (30), and 77 (78).

Ethyl 2-(1′,3′-*diacetoxy*-9′-*oxo*-9,10-*dihydroacridin*-4′-*ylmethyl*)*propenoate* (**8**). M.p. 128—130 °C (Found: C, 65.75; H, 5.4; N, 3.25. $C_{24}H_{23}NO_7$, requires C, 65.88; H, 5.30; N, 3.20%); $\nu_{max.}$ 3 000, 2 940, 1 765, 1 700, 1 640, 1 610, 1 505, 1 495, 1 400, 1 370, 1 280, 1 200, 1 170, 1 150, 1 095, 1 020, 950, 935, 880, 780, 770, and 690 cm^{-1}; δ(300 MHz) 8.28 (1 H, dd, *J* 7.9 and 1.6 Hz, 8-H), 7.67 (1 H, ddd, *J* 8.5, 7.0, and 1.6 Hz, 6-H), 7.37 (1 H, br d, *J* 8.3 Hz, 5-H), 6.81 (1 H, s, 2-H), 6.36, 5.49 (1 H each, br s, $=CH_2$), 4.30 (2 H, q, *J* 7 Hz, OCH_2Me), 3.82 (2 H, br s, $ArCH_2$), 3.74 (3 H, s, NMe), 2.49, 2.25 (3 H each, s, 2 × OCOMe), and 1.35 (3 H, t, *J* 7 Hz, OCH_2Me); *m/z* 437 (M^+, 16%), 395 (100), 352 (45), 336 (36), 322 (16), 308 (24), 280 (68), 264 (16), 252 (45), 240 (18), 228 (13), 198 (10), 149 (8), 127 (6), and 77 (14).

Preparation of 2-(1′,3′-*Dihydroxy*-9′-*oxo*-9′,10′-*dihydroacridin*-4′-*ylmethyl*)*propenoic Acid* (**9**).—Anhydrous K_2CO_3 (20 mg) was added to a solution of the diacetoxyacridone (**8**) (30 mg) in methanol (5 ml) and the mixture was heated under reflux for 15 min. The mixture was then evaporated, diluted with water, acidified with dilute HCl, and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated and the residue was crystallised from methanol–chloroform to give the dihydroxyacridone (**9**) as fine yellow needles (0.017 g, 77%), m.p. 215—217 °C (Found: M^+, 325.096. $C_{18}H_{15}NO_5$ requires *M*, 325.095; $\nu_{max.}$ 3 700—3 200, 2 940, 1 680, 1 625, 1 600, 1 575, 1 515, 1 405, 1 390, 1 260, 1 220, 1 210, 1 155, 1 130, 1 095, 825, 800, 760, and 710 cm^{-1}; δ(60 MHz) 8.26 (1 H, dd, *J* 8 and 2 Hz, 8-H), 7.83—7.10 (3 H, m, ArH), 6.40 (1 H, br s, =CH), 6.30 (1 H, s, 2-H), 5.56 (1 H, br s, =CH), and 3.81 (5 H, br s, $ArCH_2$ and N*Me*); *m/z* 325 (M^+, 100), 307 (88), 280 (90), 254 (60), 240 (20), 227 (11), 212 (12), 198 (17), 184 (8), 154 (13), 139 (11), 125 (9), 104 (10), and 77 (25).

Conversion of the Dihydroxy Acid (**9**) *into the* 3-*Methylpyranoacridone* (**1**).—The dihydroxyacridone (**9**) (0.015 g) suspended in PEG 200 (5 ml) was heated at 220 °C for 15 min. The solution was then poured into water and extracted with ether. The ether layer was washed with brine, dried, and evaporated and the crude product was subjected to preparative t.l.c. and recrystallisation from chloroform to yield (**1**) as yellow needles (0.010 g, 71%), m.p. >328 °C (decomp.). M.p., mixed m.p., i.r., ^1H n.m.r., m.s., and t.l.c. were identical with those recorded for the compound synthesized previously by heating the compound (**4**) in PEG 200 (see above).

Preparation of the Diphenylamine (**12**).[19]—*o*-Chlorobenzoic acid (5.0 g) and 3,5-dimethoxyaniline (6.5 g) were condensed in the presence of anhydrous K_2CO_3 (6.0 g) and Cu powder (0.70 g) in dry DMF at 80 °C for 6.5 h. Work-up[17] gave (**12**) as a pale green solid which on recrystallisation from ethanol–water gave pale green needles (3.64 g, 42%), m.p. 157—158 °C (lit.,[19] 147 °C).

Conversion of the Diphenylamine (**12**) *into* 4-*Formyl*-1,3-*dimethoxyacridin*-9(10H)-*one* (**13**).—The diphenylamine (**12**) (1.3 g) was slowly added (45 min at room temperature) to a well stirred mixture of dry DMF (2 ml) and $POCl_3$ (1 ml), and stirring was continued for a further 1.5 h.[7] The dark red viscous liquid was diluted with ice, and 2M NaOH solution (20 ml) was added.[20] The solution was boiled for 0.5 h and filtered. The precipitate was washed with water, dried at the pump, and recrystallized from methanol to give the formyldimethoxyacridone (**13**) as off-white needles (0.205 g, 15%), m.p. 258—260 °C (Found: C, 67.7; H, 4.75; N, 5.0. $C_{16}H_{13}NO_4$ requires C, 67.82; H, 4.62; N, 4.94%); $\nu_{max.}$ 3 620—3 320, 3 120, 2 960, 1 640, 1 620, 1 600, 1 570, 1 532, 1 470, 1 440, 1 412, 1 398, 1 370, 1 320, 1 245, 1 212, 1 150, 1 130, 990, 940, 925, 795, 778, 768, 735, and 705 cm^{-1}; δ(60 MHz) 12.83 (1 H, br s, NH), 10.13 (1 H, s, CHO), 8.13 (1 H, dd, *J* 8 and 2 Hz, 8-H), 7.86—7.10 (3 H, m, ArH), 6.13 (1 H, s, 2-H), and 4.12 and 4.07 (3 H each, s, 2 × OMe); *m/z* 283 (M^+, 100%), 266 (14), 254 (58), 237 (9), 224 (12), 211 (10), 196 (11), 183 (6), 167 (6), 154 (6), 140 (6), 126 (7), 113 (5), 91 (3), 77 (11), and 63 (7).

Methylation of Compound (**13**).[8]—Silver(I) oxide (1.0 g) and iodomethane (1 ml) were added to a well stirred solution of compound (**13**) (0.148 g) in dry DMF (20 ml) and stirring was continued for 16 h at room temperature. The reaction mixture was diluted with $CHCl_3$ (200 ml), filtered, and the solids were washed with $CHCl_3$ (50 ml). The combined organic solutions were washed with water, dried, and evaporated to dryness to give a 4-formyl-1,3-dimethoxy-10-methylacridin-9(10*H*)-one (**14**) which on recrystallisation from methanol yielded pale yellow needles (0.118 g, 76%), m.p. 218—219 °C (Found: C, 68.75; H, 5.15; N, 4.8%; *M*, 297.0997. $C_{17}H_{15}NO_4$ requires C, 68.66; H, 5.09; N, 4.71%; *M*, 297.1001); $\nu_{max.}$ 2 900, 1 670, 1 620, 1 600, 1 570, 1 495, 1 470, 1 380, 1 370, 1 300, 1 225, 1 200, 1 190, 1 135, 1 120, 1 060, 1 010, 870, 795, 770, 750, 735, and 710 cm^{-1}; δ(300 MHz) 10.34 (1 H, s, CHO), 8.40 (1 H, dd, *J* 7.9 and 1.6 Hz, 8-H), 7.68 (1 H, ddd, *J* 8.6, 7.0, and 1.6 Hz, 6-H), 7.48 (1 H, br d, *J* 8.4 Hz, 5-H), 7.32 (1 H, ddd, *J* 7.9, 7.0 and 0.7 Hz, 7-H), 6.29 (1 H, s, 2-H), 4.12, 4.07 (3 H each, s 2 × OMe), and 3.65 (3 H, s, NMe); *m/z* 297 (M^+, 100%), 280 (22), 268 (78), 250 (32), 236 (20), 225 (14), 208 (10), 196 (13), 180 (7), 167 (13), 154 (10), 139 (13), 127 (17), 119 (22), 104 (14), 89 (17), 77 (53), and 63 (27).

Conversion of Compound (**14**) *into the Monomethoxyacridone* (**15**).[9]—BCl_3 (0.1 ml) was added to a solution of the formyldimethoxyacridone (0.020 g) dissolved in CH_2Cl_2 and cooled to −10 °C, and the resulting mixture was stirred at room temperature for 15 min. It was then diluted with CH_2Cl_2, washed with water, dried, and evaporated and the resulting product recrystallised from MeOH to yield the monomethoxyacridone (**15**) as golden yellow needles (0.017 g, 89%), m.p. 229—230 °C (Found: M^+, 283.0845. $C_{16}H_{13}NO_4$ requires *M*,

283.0845); $\nu_{max.}$ 3 600—3 160br, 2 940, 2 885, 1 650, 1 620, 1 590, 1 550, 1 470, 1 455, 1 395, 1 320, 1 240, 1 205, 1 170, 1 125, 1 100, 1 065, 1 040, 965, 955, 895, 815, 790, 770, 745, 725, and 700 cm^{-1}; δ(300 MHz) 16.05 (1 H, s, OH), 10.31 (1 H, s, CHO), 8.42 (1 H, dd, *J* 8 and 1.3 Hz, 8-H), 7.81 (1 H, ddd, *J* 8.6, 7.3, and 1.3 Hz, 6-H), 7.62 (1 H, br d, *J* 8.6 Hz, 5-H), 7.42 (1 H, br t, *J* 7.6 Hz, 7-H), 6.30 (1 H, s, 2-H), 4.03 (3 H, s, O*Me*), and 3.73 (3 H, s, NCH_3); *m/z* 383 (M^+, 28%), 266 (40), 251 (10), 234 (7), 111 (24), 83 (100), 77 (10), and 55 (70).

O-Demethylation[9] *of Compound* (**14**) *to produce the Dihydroxyacridone* (**16**).—A solution of 4-formyl-*N*-methylacridone (**14**) (0.038 g) in dry CH_2Cl_2 was treated with BCl_3 (0.5 ml) at −10 °C as above and stirred for 72 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 washed with water, dried, and evaporated to dryness, and the residue purified by preparative t.l.c. (eluant: 5% toluene in $CHCl_3$, two developments) to yield essentially pure 4-formyl-1,3-dihydroxy-10-methylacridin-9(10*H*)-one (**16**) as an off-white solid (0.022 g, 64%), m.p. 228—230 °C (Found: M^+, 269.0686. $C_{15}H_{11}NO_4$ requires *M*, 269.0688); $\nu_{max.}$ 3 600—3 360br, 3 320, 2 920, 1 625, 1 620, 1 600, 1 555, 1 390, 1 370, 1 280, 1 250, 1 190, 1 135, 1 095, 1 065, 1 045, 1 025, 820, 810, 805, 770, and 705 cm^{-1}; δ(300 MHz) 15.64 (1 H, s, OH), 13.13 (1 H, s, OH), 10.01 (1 H, s, CHO), 8.46 (1 H, dd, *J* 8 and 1.5 Hz, 8-H), 7.85 (1 H, ddd, *J* 8.6, 7.4, and 1.5 Hz, 6-H), 7.57 (1 H, br d, *J* 8.6 Hz, 5-H), 7.48 (1 H, br t, *J* 7.8 Hz, 7-H), 6.22 (1 H, s, 2-H), and 4.11 (3 H, s, NMe); *m/z* 269 (M^+, 18%), 252 (22), 234 (7), 209 (6), 149 (8), 125 (12), 111 (24), 105 (32), 97 (64), 83 (66), 77 (36), 71 (74), 69 (100), and 67 (48).

Conversion of the Formyldihydroxymethylacridone (**16**) *into Hallacridone* (**2**).—Anhydrous K_2CO_3 (0.035 g) and chloroacetone (0.2 ml) were added to a solution of the formyldihydroxymethylacridone (**16**) (0.020 g) dissolved in dry acetone (10 ml) and the mixture was heated under reflux for 2 h.[10] The reaction mixture was filtered, the solids were washed with $CHCl_3$, and the combined organic solutions were evaporated. Subsequent purification of the residue by preparative t.l.c. (eluant: 1% MeOH in CH_2Cl_2, two developments) yielded hallacridone (**2**) (0.011 g, 50%), which on recrystallisation from $CHCl_3$ gave yellow needles, m.p. 295—297 °C (lit.,[2] 295—298 °C), indistinguishable (by m.p., mixed m.p., i.r., ^1H n.m.r., m.s., and t.l.c.) from an authentic sample of hallacridone[1] (Found: M^+, 307.0847. $C_{18}H_{13}NO_4$ requires *M*, 307.0845); $\nu_{max.}$ 3 700—3 200, 2 960, 1 670, 1 625, 1 600, 1 580, 1 548, 1 490, 1 460, 1 450, 1 365, 1 340, 1 300, 1 270, 1 240, 1 200, 1 140, 1 095, 1 085, 1 040, 950, 930, 810, 790, 760, 695, and 650 cm^{-1}.

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