Synthesis of Benzo[*k*]phenanthridines: Another New Approach

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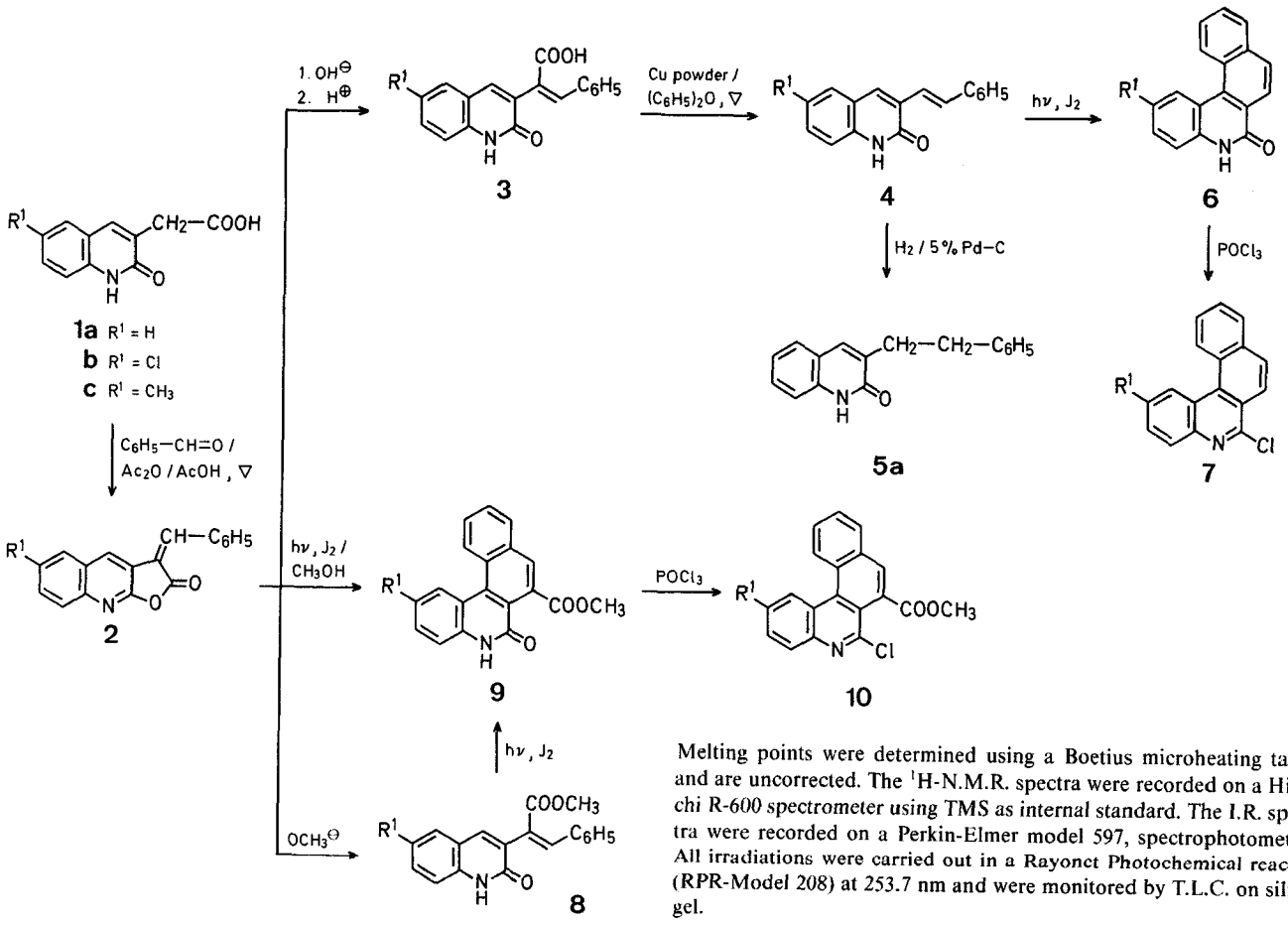
We have reported recently[1,2] two new methods for the construction of the benzo[*k*]phenanthridine system; one[1] based on the aluminium chloride-catalysed rearrangement of 4-phenyl-2,3-dihydrofuro[2,3-*b*]quinolines and the other[2] based on the photolysis of 4-phenyl-3-vinylquinolines. The precursors in both these cases were derived from 2-aminobenzophenones which, though available in different varities[3], require several steps for their preparation.

We now present another route to the title heterocycles based on construction on to 2-quinolone-3-acetic acids **1**, several of which are available through the novel two-step process, from aniline, recently[4] developed in this department. It was felt that condensation of 2-quinolone-3-acetic acid **(1)** with benzaldehyde might lead to the styrylquinolone **4** which then could be photolysed oxidatively to give the benzo[*k*]phenanthridine **(6)**. With this expectation, 2-quinolone-3-acetic acid was heated with a mixture of benzaldehyde, acetic acid, and acetic anhydride to give a product (m.p. 221–223 °C) in 72% yield. The spectral and microanalytical data are in conformity with the benzylidene-lactone structure **2a.** Compound **2a,** on warming with aqueous alkali followed by acidification, furnished an acid **3a** [m.p. 264 °C (dec)] which on decarboxylation with copper powder in diphenyl ether, gave the desired styrylquinolone **4a** (m.p. 249–252 °C). The structure **4a** was confirmed by spectral data and by its reduction to 3-(2′-phenylethyl)-quinolin-2-(1*H*)-one **(5a)** on catalytic hydrogenation over 5% palladium on carbon in ethanol.

A solution of **4a** in methanol containing a small amount of iodine was irradiated at 253.7 nm, when a product identical with authentic 6-oxo-5,6-dihydro-benzo[*k*]phenanthridine[2] **(6a)** was obtained in 84% yield. The yield is much higher than that realized by the earlier method[2] (55–60%). Further characterisation of **6a** was obtained by treating it with phosphoryl chloride to give the known 6-chlorobenzo[*k*]phenanthridine **(7a)**[2].

On warming with methanol, **2a** gave the ester **8a** which, on photolysis in the presence of iodine, gave 7-methoxycarbonyl-benzo[*k*]phenanthridone **(9a)**; this product can also be obtained in 75% yield directly from **2a** by dissolving it in methanol and then irradiating in the presence of iodine. Compound **9a** on treatment with phosphoryl chloride furnished **10a**. Thus, **2a** provided the feasibility of deriving the benzo[*k*]phenanthridines **6a, 7a, 9a,** and **10a** from it. Extension of this sequence to **1b** and **1c** likewise gave a similar series of compounds.

Use of *N*-methyl-2-quinolone-3-acetic acid **(11)** prepared from *N*-methyl-*N*-phenylaconamide gave, under the same conditions, a mixture of two components which were closely moving in T.L.C. The spectral data point to the structure **12**, perhaps as a mixture of (*Z*/*E*)-isomers. Attempts to separate them were not successful. However, photolysis of the mixture in the presence of iodine, furnished a single product (m.p. 139–141 °C) corresponding to authentic 5-methyl-benzo[*k*]phenanthridone **(13)**[5].



Melting points were determined using a Boetius microheating table and are uncorrected. The ^{1}H-N.M.R. spectra were recorded on a Hitachi R-600 spectrometer using TMS as internal standard. The I.R. spectra were recorded on a Perkin-Elmer model 597, spectrophotometer. All irradiations were carried out in a Rayonet Photochemical reactor (RPR-Model 208) at 253.7 nm and were monitored by T.L.C. on silica gel.

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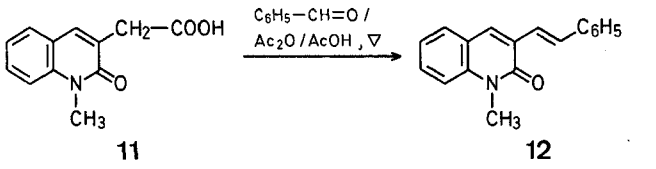
Table. Compounds **2, 3, 4, 6, 7, 8, 9,** and **10–13** prepared

Substrate	Product	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a] or Lit. m.p. [°C]	M.S. *m/e* (M^+)	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
1a[4a]	**2a**	72	221–223° ($CHCl_3$)	$C_{18}H_{11}NO_2$ (273.3)	273	1775, 1610, 1370	7.4–8.6 (m, 11H)
1b[4b]	**2b**	75	232–234° ($CHCl_3$)	$C_{18}H_{10}ClNO_2$ (307.8)	—	1770, 1610, 1380	insufficiently soluble
1c[4b]	**2c**	78	201–203° ($CHCl_3$)	$C_{19}H_{13}NO_2$ (287.3)	—	1775, 1610, 1380	2.35 (s, 3H); 7.2–8.6 (m, 10H)
2a	**3a**	82	264° (dec) (CH_3OH)	$C_{18}H_{13}NO_3$ (291.3)	—	2960 (br), 1695, 1640	insufficiently soluble
2b	**3b**	85	255° (dec) CH_3OH)	$C_{18}H_{12}ClNO_3$ (325.8)	—	2970, 1695, 1640	insufficiently soluble
2c	**3c**	86	266° (dec) (CH_3OH)	$C_{19}H_{15}NO_3$ (305.3)	—	2950 (br), 1690, 1640	insufficiently soluble
3a	**4a**	53	249–252° (C_2H_5OH/AcOH)	$C_{17}H_{13}NO$ (247.3)	247	2850 (br), 1660	insufficiently soluble
3b	**4b**	55	286–287° (C_2H_5OH/AcOH)	$C_{17}H_{12}ClNO$ (281.8)	—	2850 (br), 1660	insufficiently soluble
3c	**4c**	58	264–266° ($CHCl_3$)	$C_{18}H_{15}NO$ (261.3)	—	2860 (br), 1660	2.45 (s, 3H); 7.1–7.7 (m, 10H); 11.12 (br s, 1H)
4a	**6a**	84	286–288°	290°[2,6]	—	2970 (br), 1640	insufficiently soluble
4b	**6b**	88	>345° ($CHCl_3$)	$C_{17}H_{10}ClNO$ (279.7)	—	2990 (br), 1650	insufficiently soluble
4c	**6c**	84	307° (dec) ($CHCl_3$)	310°[2]	—	2990 (br), 1650	insufficiently soluble
6a	**7a**	87	106–108° (40–60°C PE)	109–110°[2,6]	263	—	7.3–8.5 (m, 8H); 8.8–9.2 (m, 2H)
6b	**7b**	94	187–188° (40–60°C PE)	$C_{17}H_9Cl_2N$ (298.2)	297	—	7.3–8.5 (m, 7H); 8.6–9.1 (m, 2H)
6c	**7c**	92	142–143° (40–60°C PE)	143–144°[2]	277	—	2.56 (s, 3H); 7.2–8.3 (m, 6H); 8.37 (s, 1H); 8.69 (br s, 1H); 8.9–9.2 (m, 1H)
7a	**8a**	82	198–199° (C_6H_6)	$C_{19}H_{15}NO_3$ (305.3)	305	2850 (br), 1710, 1650	3.75 (s, 3H); 7.1–8.0 (m, 10H); 8.1 (s, 1H); 12.3 (br s, 1H)
7b	**8b**	85	203–204° (C_6H_6)	$C_{19}H_{14}ClNO_3$ (339.8)	—	2825 (br), 1710, 1660	3.79 (s, 3H); 6.7–7.7 (m, 8H); 7.82 (s, 1H); 8.02 (s, 1H); 12.72 (br s, 1H)
7c	**8c**	87	189–191° (C_6H_6)	$C_{20}H_{17}NO_3$ (319.4)	—	—	2.34 (s, 3H); 3.83 (s, 3H); 6.5–7.4 (m, 9H); 7.9 (br s, 1H); 12.72 (br s, 1H)
8a	**9a**	85	270–273°	$C_{19}H_{13}NO_3$ (303.3)	303	2870 (br), 1735, 1660	4.10 (s, 3H); 7.0–8.4 (m, 8H); 8.9–9.1 (m, 1H); 11.3 (br s, 1H)
2a	**9a**	75	272–274°				
8b	**9b**	89	300–302°	$C_{19}H_{12}ClNO_3$ (337.8)	—	2850 (br), 1730, 1660	—
2b	**9b**	77	300–301°				
8c	**9c**	84	289–291°	$C_{20}H_{15}NO_3$ (317.4)	—	2870 (br), 1730, 1660	2.58 (s, 3H); 4.11 (s, 3H); 7.1–8.1 (m, 6H); 8.45 (br s, 1H); 8.9–9.1 (m, 1H); 11.35 (br s, 1H)
2c	**9c**	72	288–291°				
9a	**10a**	90	150–152° (C_6H_6)	$C_{19}H_{12}ClNO_2$ (321.8)	—	—	4.00 (s, 3H); 7.4–8.4 (m, 7H); 8.7–9.0 (m, 2H)
9b	**10b**	94	200–201° (C_6H_6/40–60°C PE)	$C_{19}H_{11}Cl_2NO_2$ (356.2)	—	—	4.12 (s, 3H); 7.4 (s, 1H); 7.6–8.5 (m, 5H); 8.8–9.2 (m, 2H)
9c	**10c**	91	208–210° (C_6H_6/40–60°C PE)	$C_{20}H_{14}ClNO_2$ (335.7)	—	—	2.57 (s, 3H); 4.01 (s, 3H); 7.4–8.3 (m, 6H); 8.65 (br s, 1H); 8.8–9.0 (m, 1H)
—	**11**	63	174–176° (CH_3OH)	$C_{12}H_{11}NO_3$ (217.2)	—	2990 (br), 1705, 1605	3.78 (s, 2H); 3.85 (s, 3H); 7.3–7.9 (m, 5H); 8.1–8.5 (br s, 1H)
11	**12**	75	170° (dec); 230°	$C_{18}H_{15}NO$ (261.3)	—	2950 (br), 1690, 1635, 1615	3.5–4.3 (dd, J=7 Hz, 5H); 6.8–8.0 (m, 10H)
12	**13**	65	139–141° (CH_3OH)	140–141°[5,6]	—	—	—

[a] Satisfactory microanalyses obtained: C ±0.26, H ±0.25.



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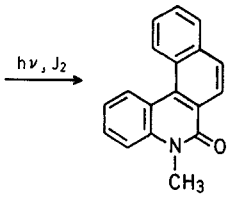

13

Benzylidene-lactones 2a–c:
A mixture of 2-quinolone-3-acetic acid (**1a**; 0.04 mol), benzaldehyde (0.045 mol), acetic acid (20 ml), and acetic anhydride (20 ml) is refluxed for 6 h. The excess reagents are removed under reduced pressure and the resulting yellow coloured solid is filtered, washed with sodium hydrogen sulfite solution, and finally with water. The dried solid is chromatographed over silica gel with benzene/ethyl acetate (3 : 1) to furnish the benzylidene-lactone **2a** as yellow needles. Similar treatment of acids **1b** and **1c** led to the lactones **2b** and **2c**, respectively (Table).

α-(2-Quinolon-3-yl)-cinnamic acids 3a–c:
The lactone **2a** (0.5 g) is mixed with 10% aqueous sodium hydroxide solution (200 ml) and stirred overnight. It is then filtered and the filtrate acidified to furnish the acid **3a**. Likewise **2b** and **2c** gave rise to the acids **3b** and **3c**, respectively (Table).

3-Styrylquinolin-2-(1*H*)-ones 4a–c:
The acid **3a** (0.5 g) is heated with copper powder (0.4 g) in diphenyl ether under reflux for 5 h. Removal of the solvent under reduced pressure leaves a residue which, when chromatographed over silica gel using benzene/ethyl acetate (3 : 1) as eluent, furnishes **4a**, as yellow needles. Similar treatment of **3b** and **3c** led to the styrylquinolones **4b** and **4c**, respectively (Table).

Hydrogenation of 4a with 5% Palladium on Carbon:
A solution of **4a** (100 mg) in ethanol (100 ml) is shaken with 5% palladium on carbon (20 mg) under hydrogen at 2 atm pressure for 1 h, filtered, the filtrate is concentrated, and cooled to give colourless needles of 3-(2-phenylethyl)-quinolin-2-(1*H*)-one **(5a)**; yield: 71 mg (72%); m.p. 184–185 °C.

$C_{17}H_{15}NO$	calc.	C 81.91	H 6.07
(249.3)	found	81.69	5.93

M.S.: $m/e = 249$.

I.R. (KBr): $\nu = 1645$ cm^{-1} (—NH—CO—).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.04$ (s, 4H); 6.8–8.0 (m, 10H); 11.95 ppm (br s, 1H).

6-Oxo-5,6-dihydrobenzo[*k*]phenanthridines 6a–c:
A methanol solution (200 ml) containing **4a** (200 mg) and iodine (30 mg) is irradiated for 18 h. The product obtained after evaporation of the solvent is chromatographed over silica gel with benzene/ethyl acetate (2 : 1). Similar treatment of **4b** and **4c** led to the benzo[*k*]phenanthridines **6b** and **6c**, respectively (Table).

6-Chlorobenzo[*k*]phenanthridines 7a–c:
The phenanthridine **6a** (200 mg) is treated with phosphoryl chloride (6 ml) according to Ref.[6]. The product obtained after work up is chromatographed over basic alumina with benzene/petroleum ether (1 : 1) to furnish **7a** as colourless needles. Similar treatment of **6b** and **6c** led **7b** and **7c**, respectively (Table).

Methyl α-(2-Quinolon-3-yl)cinnamates 8a–c:
A mixture of the lactone **2a** (500 mg), absolute methanol (20 ml), and one drop of concentrated hydrochloric acid is refluxed for 3 h. The excess solvent is removed, and the residue is washed with water, and dried to give **8a**. The lactones **2b** and **2c** likewise led to **8b** and **8c**, respectively (Table).

Methyl 6-Oxo-5,6-dihydrobenzo[*k*]phenanthridine-7-carboxylates 9a–c:
Method A: A methanol solution (100 ml) containing **8a** (100 mg) and iodine (20 mg) is irradiated for 9 h. The product obtained after work up is chromatographed over silica gel with benzene/ethyl acetate (2 : 1) to give **9a** as pale yellow crystals. Similar treatment of **8b** and **8c** gave rise **9b** and **9c**, respectively (Table).

Method B: A solution of **2a** (100 mg) in methanol (200 ml) is irradiated for 12 h in the presence of iodine (20 mg). The product obtained after work up is chromatographed over silica gel with benzene/ethyl acetate (2 : 1) to give **9a** as pale yellow crystals. Irradiation of **2b** and **2c** led similarly to **9b** and **9c**, respectively (Table).

Methyl 6-Chlorobenzo[*k*]phenanthridine-7-carboxylates 10a–c:
Compound **9a** is treated[6] with phosphoryl chloride and the product obtained after workup is chromatographed over alumina (basic) with benzene/petroleum ether (2 : 1) to furnish **10a**. The phenanthridines **9b** and **9c** likewise led to **10b** and **10c**, respectively (Table).

***N*-Methyl-2-quinolone-3-acetic Acid (11):**
A solution of aconyl chloride prepared from aconic acid (8 g) is added dropwise with stirring to an ice-cold mixture of *N*-methylaniline (6.3 ml) and dry pyridine (5.1 ml) in anhydrous benzene (100 ml). After the addition, the mixture is stirred for a few minutes and then poured into water (300 ml). The benzene layer is separated, washed successively with dilute hydrochloric acid, aqueous sodium carbonate solution, and with water. Evaporation of the solvent furnishes a viscous mass. The viscous mass is heated with polyphosphoric acid (100 ml) at 125–130 °C for 5 h under exclusion of moisture. Then it is cooled and poured in to ice/water. The solid that separates is collected, dissolved in aqueous 5% sodium hydroxide solution, and then acidified to give pure *N*-methyl-2-quinolone-3-acetic acid **(11)** (Table).

3-Styryl-*N*-methyl-2-quinolone (12):
N-Methyl-2-quinolone-3-acetic acid (0.04 mol) is condensed with benzaldehyde (0.045 mol) under the same conditions as used for **1a**. The solid that is isolated after workup is chromatographed over silica gel using benzene/ethyl acetate (1 : 1) to give **12** (Table).

***N*-Methylbenzo[*k*]phenanthridone (13):**
A methanolic solution containing **12** (200 mg/200 ml) and iodine (125 mg) is irradiated for 18 h. Then T.L.C. analysis shows only a single product. Evaporation of the solvent and chromatography of the residue over silica gel with benzene/ethyl acetate (1 : 1) furnishes *N*-methylbenzo[*k*]phenanthridine **(13)** (Table).

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