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Synthesis of Some Quinolizine Derivatives

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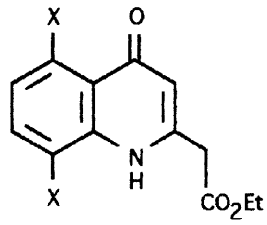
Abstract: Fused quinolizines have been formed from ethyl 2-(1,4-dihydro-4-oxoquinolin-2-yl)acetate by (a) Michael addition reactions of the sodium salt with alkynes (cyclization onto N occurs without isolation of the intermediate) and (b) Knoevenagel reaction with aryl aldehydes and thermal cyclization of the intermediates.

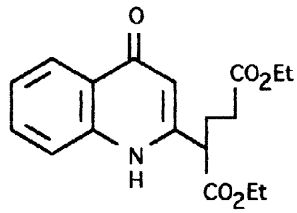
INTRODUCTION

We have previously prepared a number of intermediates by Michael addition of **1a** (at C-α) to various substituted alkenes and alkynes, and studied their further cyclization;[1] C-3 and N-1 are potential sites for ring closure. The finding was that where the intermediate could cyclize to form a saturated 6-membered ring, as in **2**, cyclization was onto C-3, in this case to form **3**. Saturated 6-membered ring formation onto N-1 was not observed. On the other hand, if there was a choice of 5 or 6-membered ring formation, the former was preferred and occurred onto N-1.



1

a X = H **b** X = MeO



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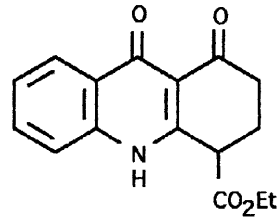

3

If the side-chain in **2** was unsaturated, cyclization was onto N-1 irrespective of ring size. Thus reaction of **1a** with diethyl acetylenedicarboxylate gave **4** while the only example of 6-membered ring formation onto N-1 came from **5**. Here, **6** was readily formed and this kinetically favoured product could be thermally isomerized to **7**.

This interesting difference between saturated and unsaturated side-chains with respect to 6-membered ring formation has prompted us to investigate some further examples of the latter type. Two types of reactions were investigated; a range of compound types were produced but annulation of the 6-membered ring was always onto N-1.

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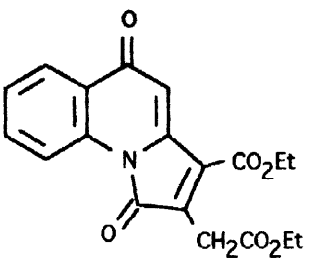

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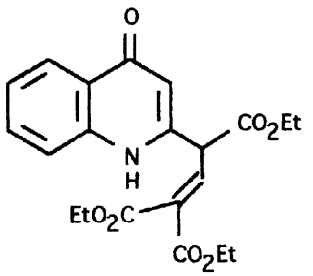

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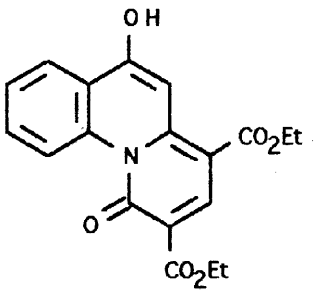
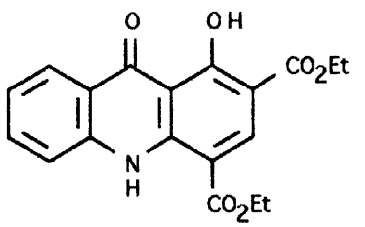


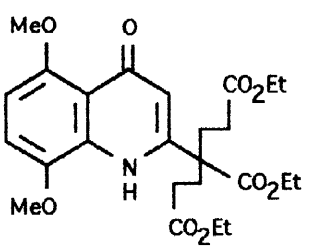
6



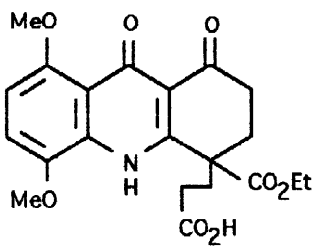
7

RESULTS AND DISCUSSION

Firstly, as a further illustration of the preference for C-3 cyclization when a six-membered saturated ring was possible, compound **8**, obtained as a byproduct from Michael addition of ethyl acrylate to **1b**, was readily cyclized in hot polyphosphoric acid to give **9**. No evidence for additional closure onto N-1 was seen.[2]



8

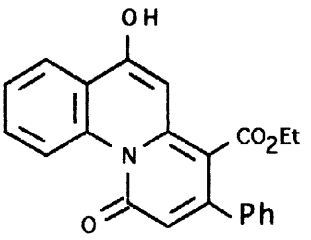


9

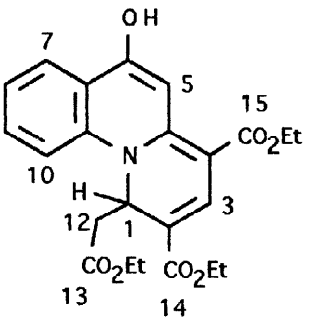
Reaction with alkynes.

The preformed sodium salt of **1a** underwent Michael addition with alkynes in DMSO, and subsequent cyclization occurred in the one-pot. Two analogues of the diethyl acetylenedicarboxylate studied previously[1] were reacted with **1a**; interestingly, each gave a different type of product and each was different from the **4** observed before.

One mole equivalent of ethyl phenylpropiolate was incorporated into **1a** by way of unexceptional conjugate addition and cyclization to give **10**. This structure followed from the existence of H-5 and downfield shift for H-10 in the ^{1}H NMR spectrum and this yellow product is analogous to that formed from EMME (**6**).



10



11

Ethyl propiolate, however, gave a different reaction in that two molar equivalents were involved and the orange product, formed in high yield, was assigned structure **11** on the basis of ^{1}H and ^{13}C 1D and 2D NMR experiments (summarized in Table 1). Ring closure onto N followed from the existence of H-5. The configuration about C-1 followed mainly from the numerous $^{3}J_{CH}$ couplings observed for H-1, while the ^{1}H NMR spectrum showed that this H was adjacent to the CH_2 labelled 12. This product can be envisaged as following from a double conjugate addition, with six-membered ring formation then favoured in the final cyclization. The presence of the bulky phenyl group in the preceding phenylpropiolate reaction no doubt precludes this double conjugate addition.

Table 1. NMR data[A] for compound **11** in $CDCl_3$

	^{13}C		13	15	14	6	4a	10a	3	9	8	7	6a	10	2	5	4	1	12
^{1}H			170.0	168.3	165.3	159.6	151.5	139.0	136.7	131.7	123.8	123.7	120.2	114.9	105.0	100.3	92.8	50.7	37.4
12	2.60	m[B]	+												+			+[C]	o
1	6.57	t[B]	+		+		+	+	+						+			o	+[C]
8	7.36	t									o		+	+					
9	7.65	t						+		o		+							
10	8.00	d									+		+	o					
3	8.07	s		+	+		+		o									+	
7	8.11	d				+		+		+		o							
5	8.52	s[D]				+	+						+			o	+		

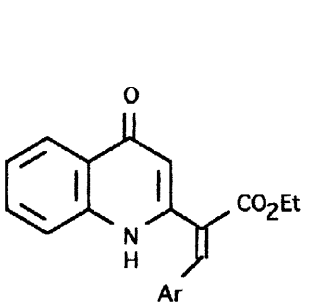
o $^{1}J_{CH}$ (HETCOR) + $^{3}J_{CH}$ (HMBC)

[A] Other peaks. ^{1}H: 12.10 (br s, OH), 4.2-4.32 (m, 2 x OCH_2), 3.7-3.85 (m, OCH_2), 1.3-1.45 (2 x t, 2 x CH_3) 1.00 (t, CH_3). ^{13}C: 60.8, 60.5, 60.1 (OCH_2), 14.5 (2 x CH_3), 13.7 (CH_3).
[B] Coupled. [C] $^{2}J_{CH}$ [D] Exchanges with D_2O.

Reaction with aldehydes.

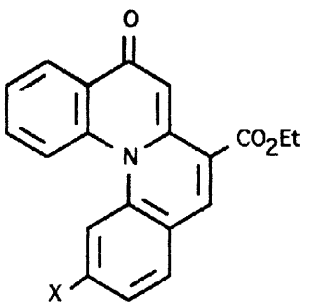
In a quite different type of reaction, a Knoevenagel condensation in mild acid conditions between **1a** and 2,4-dichlorobenzaldehyde gave the intermediate **12a** (88%), again containing unsaturation in the side-chain. Then, reflux in diphenyl ether gave cyclization by displacement of the ortho chlorine group to give **13a** (85%).

Cyclization was evident from the changed ^{1}H NMR pattern for the chloroaryl ring from that in **12a**, while the appearance of three singlets was only consistent with cyclization onto N.



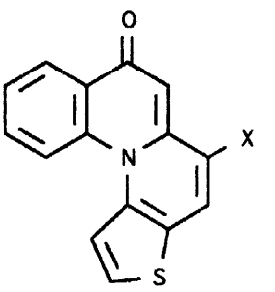
12

a Ar = 2,4-$Cl_2C_6H_3$
b Ar = 2-$NO_2C_6H_4$
c Ar = 3-bromo-2-thieno



13

a X = Cl
b X = H



14

a X = CO_2Et
b X = H

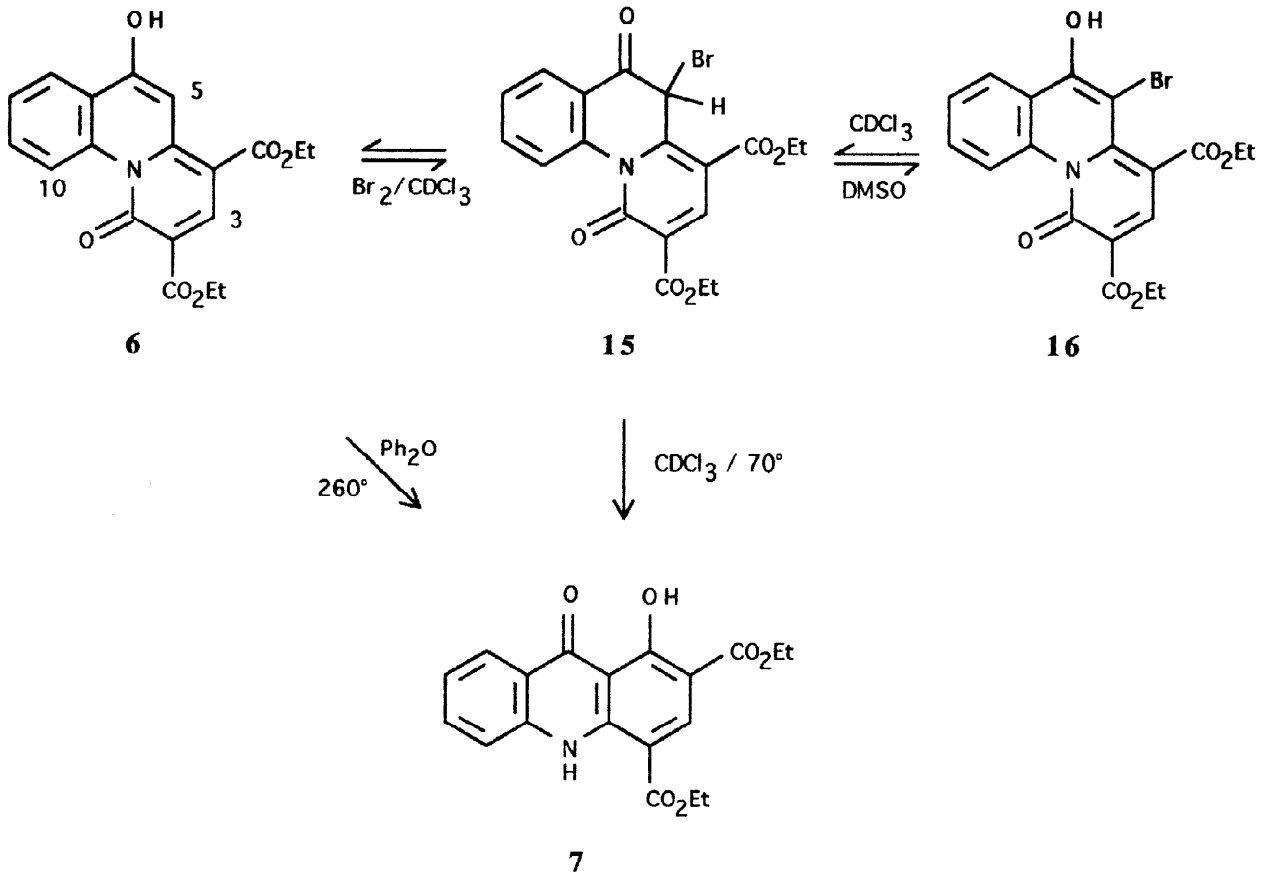
In order to check on the potential generality of this interesting reaction, we briefly investigated two aspects. A nitro group was considered as a leaving group and the same reactions with o-nitrobenzaldehyde gave **13b** though the condensation intermediate **12b** was obtained in only 28% yield. In an extension to another type of aromatic aldehyde, 3-bromothiophene-2-carbaldehyde gave the new ring system **14**. Chromatography was required to obtain the product in this case. As well as **14a**, the analogue of compounds **13**, a sample of **14b** was also isolated, in which the ester function had been lost.

Bromination studies.

We looked at some bromination reactions, in NMR tubes in $CDCl_3$, of the hydroxyquinazolines **6** and **11**. Hydroxyquinolizinium salts[3] and quinolizinones[4] are activated to electrophilic substitution and give the expected products from reactions such as bromination. The reaction of **6** is summarized in Scheme 1, and had some unusual features.

H-5 of compound **6** (in $CDCl_3$ solution) underwent rapid exchange with D_2O. Bromination in this solvent also occurred immediately at this position and the product was assigned structure **15** from NMR analysis. In the ^{1}H spectrum, H-5 was a singlet at δ 6.85 ppm. This is due to a marked deshielding effect as a HETCOR[5] experiment established that it was attached to a carbon at δ 37.9. This is a remarkable difference in the signal positioning in ^{1}H and ^{13}C spectra and we are unaware of any example with a greater difference. A similar phenomenon, but with a smaller difference, was noted for H-1/C-1 in **11**. Structure **15** is interesting as it is a rare example of a keto tautomer being formed in bromination of a "phenol".

When the bromination of **6** was carried out in DMSO-d_6, another product formed and this was assigned as **16**, the expected substitution product, and tautomer of **15**. The NMR signal for H-5 was absent and there were no peculiarities in the spectra. However, when a small sample of this solution was diluted with $CDCl_3$, **15** was formed completely.



6 **15** **16**

7

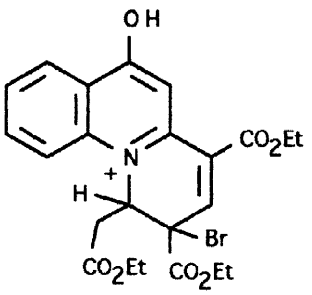
Scheme 1

When an attempt was made to isolate **16** by addition of water, extraction with $CDCl_3$ gave a clean mixture of **6** and **7**, i.e., a facile electrophilic replacement of bromine occurred either by hydrogen (to give **6**) or by carbon to give the rearranged product **7**. Compound **7** was known to us and was previously obtained by heating **6** in diphenyl ether.[6] Now, a $CDCl_3$ solution of **15** heated to only 70° for 2.5 h gave complete conversion to **7**, while **6** was unchanged in these conditions in 16 h (a 30% conversion from **6** occurred in DMSO at 120° in 6 h). As a further example of the instability of **15**, electrospray mass spectrometry of it in $CDCl_3$ solution (with CH_2Cl_2 as mobile phase) gave no evidence for **15**, but had a 100% peak at m/z 356 corresponding to the debromo species **6** or **7**.

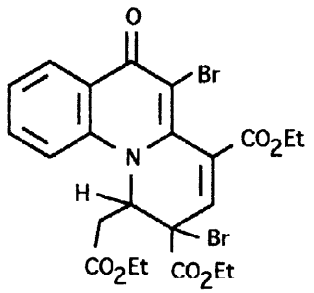
CPK models of **15** and **16** indicate substantial interactions between the bromine and 3-ester in each and the resultant strain is apparently manifested in a marked weakening of the N-C1 bond. Bromination of the highly activated ring therefore provides an alternative low energy pathway for rearrangement of **6** to the thermodynamically more stable **7**.

Bromination of **11** followed a different course. The initial reaction in $CDCl_3$ was again rapid, but not at C-5 since singlets for H-3 and H-5 were still present in the ^1H NMR spectrum. However, one of the low-field quaternary carbon signals of 11 had been replaced by a new one at 52.4 ppm and the electrospray mass spectrum was in accord with a monobromo compound. This information is consistent with **17** through reaction at C-2 (though it could be the C-4 isomer). The addition of more bromine had no effect, consistent with the depiction of **17** as a quinolizium species, but if the solution was washed with bisulfite bromination at C-5 now occurred. The electrospray mass spectrum showed a dibromo compound and this has been assigned structure **18**. The main

effect of the bisulfite is probably as a weak base to generate the quinolizine species, activated to electrophilic substitution.



17



18

In summary, we have confirmed that cyclization of intermediates derived from **1a** and containing unsaturation in the side-chain occurs onto N, and the reactions described provide entry to a diverse range of benzo[*c*]quinolizine derivatives.

EXPERIMENTAL

General.

NMR spectra were run on a Brüker 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.[5] 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 $t1$ 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).

The long range proton detected (three-bond) (^1H-^{13}C) heteronuclear multiple bond correlation (HMBC) experiment on 11 was carried out on a Brüker DRX-400 (400.13 and 100.62 MHz for ^1H and ^{13}C, respectively) spectrometer, equiped with Grasp II z-gradient system and used the pulse sequence described by Bax and Summers[7]. The low pass J-filter portion was set for an average one-bond heteronuclear coupling of 150 Hz (3.3 ms). The long range delay utilized to excite the heteronuclear multiple quantum coherence was set for 8.3 Hz (60 ms). The spectrum was acquired as 2K x 600 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 32. Spectral widths were 25062 Hz in F_1 (^{13}C) and 5208 Hz in F_2 (^1H). The 90° pulse widths were 11.2 (^1H) and 10.7 (^{13}C) μs, and a 2 s interpulse delay was employed.

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. Electron impact mode high-resolution mass spectra were obtained by Dr N. Davies, University of Tasmania. Column chromatography was carried out on silica.

Diethyl 4-Ethoxycarbonyl-4-(5,8-dimethoxy-4-oxo-1,4-dihydroquinolin-2-yl)heptane-1,7-dioate (8). This was isolated by chromatography (ethyl acetate, R_f 0.3) as a byproduct of the reaction of ethyl acrylate with **1b**,[1] mp 135-136° (from ethyl acetate). ^{1}H NMR δ 0.93 (t, J = 7.1 Hz, 2 x CH_3), 1.06 (t, J = 7.1 Hz, CH_3), 1.9-2.35 (m, 8H), 3.67 (s, OCH_3), 3.72 (s, OCH_3), 3.79 (q, J = 7.1 Hz, 2 x OCH_2), 4.04 (q, J = 7.1 Hz, OCH_2), 6.15 (s), 6.37 (d), 6.70 (d). ESMS: m/z 492 (M+1). Anal. Calcd for $C_{20}H_{25}NO_8$: C, 59.0; H, 6.2; N, 3.4. Found: C, 58.7; H, 6.5; N, 3.4%.

(5,8-Dimethoxy-4-ethoxycarbonyl-1,9-dioxo-1,2,3,4,9,10-hexahydro)-4-acridinepropanoic acid (9) Compound **8** with 5 times its weight of polyphosphoric acid was heated at 110° for 16 h then poured onto ice. The pH was taken to 5-6 with 10% sodium hydroxide solution and $CHCl_3$ extraction gave the crude product. Chromatography (ethyl acetate, R_f 0.13) gave the yellow **9**, mp 148-151° (from ethyl acetate/light petroleum (bp 60-90°)) in 37% yield. ^{1}H NMR δ 1.17 (t, J = 7.1 Hz, CH_3), 2.15-2.9 (m, 8H), 3.92 (s, OCH_3), 3.93 (s, OCH_3), 4.14 (q, J = 7.1 Hz, OCH_2), 6.78 (d), 7.09 (d). ^{13}C NMR δ 13.9 (CH_3), 30.6 (CH_2), 31.3 (CH_2), 34.3 (CH_2), 52.1 (C), 56.5 (CH_3), 56.9 (CH_3), 60.4 (CH_2), 61.8 (CH_2), 106.3 (CH), 109.3 (C), 112.2 (C), 114.3 (CH), 141.7 (C), 146.8 (C), 152.7 (C), 160.1 (C), 171.2 (C), 172.9 (C), 176.3 (C), 203.7 (C). EIMS (M^+) Found: 417.14288. Calcd for $C_{21}H_{23}NO_8$: 417.14244.

Ethyl [2,4-Di(ethoxycarbonyl)-6-hydroxy-(1*H*)-benzo[*c*]quinolizin-1-yl] acetate (11). Compound **1a** (0.11 g, 0.5 mmol) was dissolved in 0.5 M ethanolic sodium ethoxide (2 ml, 1 mmol). The ethanol was evaporated at reduced pressure, dry DMSO (2 ml) and ethyl propiolate (0.1 g, 1 mmol) were added and the mixture was stirred at room temperature for 2 h. Water (10ml) was added and the pH was taken to 3 with 10% HCl. The mixture was extracted with $CHCl_3$ (3 x 10 ml), and the extracts were washed with water (2 x 10 ml), dried ($MgSO_4$) and the solvent was evaporated. Column chromatography (ethyl acetate) gave **11**, R_f = 0.8, as an orange solid (0.18 g, 90%), mp 145-146° (from ethyl acetate). ^{1}H and ^{13}C NMR, see Table 1. ESMS: m/z 428 (M+1). Anal. Calcd for $C_{23}H_{25}NO_7$: C, 64.6; H, 5.9; N, 3.3. Found: C, 64.4; H, 6.1; N, 3.0%.

Ethyl 6-Hydroxy-1-oxo-3-phenyl-(1*H*)-benzo[*c*]quinolizine-4-carboxylate (10). This was prepared as for **11**, from **1a** and ethyl phenylpropiolate (1 mol equivalent). The reaction time was 3 h at room temperature and the product was obtained in 70% yield as a yellow solid, mp 237-238° (from $CHCl_3$). ^{1}H NMR (DMSO-d_6) δ 0.73 (t, J = 7.0 Hz, CH_3), 3.85 (q, J = 7.0 Hz, OCH_2), 6.23 (s, 1H), 7.14 (s, 1H), 7.3-7.4 (m, 5H, phenyl), 7.56 (m, 2H), 8.05 (m, 1H), 9.62 (d, J = 8.5 Hz, 1H), 11.70 (s, OH). ^{13}C NMR (DMSO-d_6) δ 13.1 (CH_3), 60.6 (OCH_2), 97.9 (CH), 105.2 (C), 110.5 (CH), 121.1 (C), 121.8 (CH), 121.9 (CH), 126.2 (CH), 126.7 (CH), 128.2 (CH), 128.7 (CH), 136.4 (C), 139.4 (C), 144.4 (C), 150.1 (C), 156.0 (C), 162.4 (C), 167.5 (C). ESMS: m/z 360 (M+1). Anal. Calcd for $C_{22}H_{17}NO_4.0.5H_2O$: C, 71.7; H, 4.9; N, 3.8. Found: C, 72.0; H, 4.7; N, 3.7%.

Bromination experiments.

These were carried out in NMR tubes by the addition of, initially, 1 mol equivalent of 0.1 M Br_2 in CCl_4 to a solution of **6** or **11** in $CDCl_3$. Spectra were recorded at times described in the text. With one exception, the products were not isolated and the relevant spectral data are as follows (those for **6**[1] and the final **7**[6] have been published):

15: ^{1}H NMR δ 6.85 (s, H-5), 7.49 (t), 7.73 (t), 7.89 (d), 8.38 (d), 8.57 (s, H-3). ^{13}C NMR δ 37.9 (CH), 109.6 (C), 122.8 (C), 124.7 (C), 125.4 (CH), 127.1 (CH), 128.5 (CH), 134.7 (CH), 136.6 (C), 143.2 (CH), 149.5 (C), 158.2 (C), 163.0 (C), 163.5 (C), 185.8 (C).

16: ^{1}H NMR (DMSO-d_6) δ 7.46 (t), 7.77 (t), 7.94 (s, H-3), 7.99 (d), 8.41 (d).^{13}C NMR (DMSO-d_6) δ 117.6 (C), 123.1 (CH), 125.6 (C), 127.3 (CH), 128.0 (CH), 128.2 (C), 134.8 (CH), 138.4 (C), 138.6 (C), 138.9 (CH), 157.5 (C), 162.8 (C), 165.8 (C), 172.3 (C), 175.0 (C).

17: ^{1}H NMR δ 2.88 (qd, 2H, H-12), 6.28 (t, J = 4.8 Hz, H-1), 7.88 (t), 8.03 (s), 8.21 (t), 8.55-8.59 (m, 2H), 8.62 (s). ^{13}C NMR δ 13.9 (CH_3), 14.1 (CH_3), 14.4 (CH_3), 36.7 (CH_2), 52.4 (C), 59.2 (CH), 62.2 (CH_2), 63.9 (CH_2), 64.7 (CH_2), 108.4 (CH), 117.7 (CH), 121.3 (C), 125.9 (CH), 128.5 (CH), 128.9 (C), 137.1 (CH), 140.3 (C), 140.7 (CH), 144.4 (C), 161.5 (C), 164.7 (C), 168.5 (C), 171.1 (C). ESMS: m/z 506 (88%), 507 (20), 508 (100), 509 (20), 510 (5), 511 (2) (all M+1 for $C_{23}H_{24}BrNO_7$).

18: This was formed when 2.5 mol equivalents of the bromine solution was added to **11**. The mixture was stirred at room temperature for 10 min, then washed with 10% sodium bisulfite solution, and dried. Column chromatography (ethyl acetate/hexane, 1:1) gave a sample of **18**, R_f 0.83. ^{1}H NMR δ 2.58-2.76 (qd, 2H, H-12), 5.81 (t, J = 5.1 Hz, H-1), 7.43 (t), 7.48 (s, H-3), 7.75 (t), 8.00 (d), 8.48 (d). ^{13}C NMR δ 13.6 (CH_3), 13.8 (2 x CH_3), 37.0 (CH_2), 52.7 (C), 58.8 (CH), 61.8 (CH_2), 62.8 (CH_2), 64.0 (CH_2), 110.3 (C), 115.5 (CH), 124.0 (C), 124.8 (CH), 127.8 (CH), 133.6 (CH), 135.1 (C), 136.0 (CH-3), 137.9 (C), 139.7 (C), 164.1 (C), 165.7 (C), 166.8 (C), 172.6 (C). ESMS: m/z 584 (50%), 585 (14), 586 (100), 587 (24), 588 (54), 589 (13) (all M+1 for $C_{23}H_{23}Br_2NO_7$).

Reaction of 1a with aldehydes

A mixture of **1a** (5 mmol), aldehyde (5 mmol), ammonium acetate (0.05 g) and acetic acid (0.3 ml) in benzene (20 ml) was heated under reflux for 24 h. The benzene was distilled off and the residue was crystallized to give the intermediate **12**. This was heated under reflux in diphenyl ether (1 ml/mmol of **12**) for 24 h, cooled and diluted with light petroleum (bp 60-90°) to give the products **13** and **14**. In this way the following were prepared:

From 2,4-dichlorobenzaldehyde. **Ethyl 3-(2,4-Dichlorophenyl)-2-(1,4-dihydro-4-oxoquinolin-2-yl)propenoate (12a)** (88%), mp 270-271° (from dimethyl formamide. ^{1}H NMR (DMSO-d_6) δ 1.23 (t, J = 7.0 Hz, CH_3), 4.27 (q, J = 7.0 Hz, OCH_2), 5.78 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 7.29-7.35 (m, 2H), 7.51 (d, J = 8.2 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 7.76 (d, J = 1.2 Hz, 1H), 8.02-8.06 (m, 2H), 12.0 (s, NH). ^{13}C-NMR (DMSO-d_6) δ14.1 (CH_3), 61.8 (CH_2), 110.1 (CH), 118.5 (C), 123.6 (CH), 124.9 (CH), 127.6 (CH), 129.5 (CH), 129.8 (C), 130.8 (CH), 130.9 (CH), 132.1 (CH), 134.9 (CH), 135.4 (C), 138.8 (C), 140.3 (C), 144.8 (C), 149.8 (C),164.5 (C), 176.6 (C). ESMS: m/z 388 (100), 389 (23), 390 (68), 391 (14), 329 (12) (all M+1).

Ethyl 8*H*-2-Chloro-8-oxodibenzo[*c*,*f*]quinolizine-6-carboxylate (13a). A brown solid (85 %), mp 220-222° (from ethanol). ^{1}H NMR[8] δ 1.39 (t, J = 7.1 Hz, CH_3), 4.39 (q, J = 7.1 Hz, OCH_2), 7.29 (dd, J=8.2, 1.6Hz, H-3), 7.30 (s, H-7), 7.55 (t, J = 7.5 Hz, H-11), 7.56 (d, J = 8.2 Hz, H-4), 7.65 (td, J =7.8, 1.6 Hz, H-10), 8.00 (d, J = 1.6 Hz, H-1), 8.02 (s, H-5), 8.09 (d, J = 8.4 Hz, H-9), 8.41 (dd, J = 7.9, 1.6 Hz, H-12). ^{13}C NMR δ 14.2 (CH_3), 62.1 (OCH_2), 109.6 (C-7), 119.7 (C-1), 120.8 (C-9), 121.8 (C), 124.7 (C), 125.5 (C-3), 126.3 (C-12), 126.5 (C-11), 129.6 (C), 130.5 (C-10), 130.7 (C-4), 135.5 (C-5), 137.5 (C), 138.6 (C), 138.8 (C), 142.5 (C), 164.0 (C), 176.9 (C). ESMS: m/z 352 (100), 353 (22), 354 (35), 355 (7), all (M+1). Anal. Calcd for $C_{20}H_{14}ClNO_3$: C, 68.3; H, 4.0; N, 4.0. Found: C, 68.3; H, 3.7; N, 3.8.

From o-nitrobenzaldehyde. **Ethyl 2-(1,4-Dihydro-4-oxoquinolin-2-yl)-3-(2-nitrophenyl)propenoate (12b)**. This was obtained in 28% yield by chromatography (ethyl acetate) of the

crude product, $R_f = 0.1$, mp 226-228° (from ethyl acetate). ^1H NMR ($CDCl_3$+DMSO-d_6) δ 1.01 (t, J = 7.1 Hz, CH_3), 4.02 (q, J = 7.1 Hz, OCH_2), 5.70 (s, 1H), 6.92 (d, J = 6.7 Hz, 1H), 7.01 (t, J = 5.8 Hz, 1H), 7.08-7.29 (m, 4H), 7.82 (d, J = 7.4 Hz, 1H), 7.88 (d, J = 8.12 Hz, 1H), 8.05 (s, 1H), 11.76 (br s, NH). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 13.9 (CH_3), 61.7 (OCH_2), 110.9 (CH), 118.3 (CH), 123.5 (CH), 124.4 (C), 124.7 (CH), 124.9 (CH), 128.9 (C), 130.0 (CH), 130.4 (CH), 131.7 (CH), 133.8 (CH), 140.1 (C), 141.7 (CH), 144.9 (C), 147.1 (C), 164.4 (C), 177.2 (C). ESMS: m/z 365 (M+1).

Ethyl 8*H*-8-Oxodibenzo[*c*,*f*]quinolizine-6-carboxylate (13b). A brown solid (65%), mp 183-186° [from toluene/light petroleum (bp 90-110°), which could not be freed of minor impurities. ^1H NMR δ 1.37 (t, J = 7.1 Hz, CH_3), 4.36 (q, J = 7.1 Hz, OCH_2), 7.26 (s, 1H), 7.29 (d, J = 7.4 Hz, 1H), 7.43-7.60 (m, 4H), 7.93 (d, J = 8.5 Hz, 1H), 8.02 (s, 1H), 8.08 (d, J = 8.4 Hz, 1H), 8.38 (dd, J = 7.9, 1.6 Hz, 1H). ^{13}C NMR δ 14.2 (CH_3), 61.9 (OCH_2), 108.9 (CH), 119.8 (CH), 121.2 (CH), 123.2 (C), 124.4 (C), 125.0 (CH), 126.0 (CH), 129.5 (C), 129.7 (CH), 130.0 (CH), 131.3 (CH), 136.4 (CH), 137.7 (C), 138.7 (C), 142.7 (C), 164.2 (C), 176.6 (C). ESMS: m/z 318 (M+1).

From 3-bromothiophene-2-carbaldehyde. **Ethyl 3-(3-bromo-2-thieno)-2-(1,4-dihydro-4-oxoquinolin-2-yl)propenoate (12c).** (84%), mp 268-271° (from ethanol). ^1H NMR ($CDCl_3$+DMSO-d_6) δ1.20 (t, J = 7.1 Hz, CH_3), 4.19 (q, J = 7.1 Hz, OCH_2), 6.14 (s, 1H), 6.96 (d, J = 5.3 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 5.3 Hz, 1H), 7.45-7.56 (m, 2H), 8.14 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H). ^{13}C NMR ($CDCl_3$+DMSO-d_6) δ 14.0 (CH_3), 61.3 (OCH_2), 110.6 (CH), 118.4 (CH), 119.1 (C), 123.3 (CH), 124.1 (C), 125.0 (CH), 125.1 (C), 130.0 (CH), 130.7 (C), 131.5 (CH), 132.5 (CH), 133.9 (CH), 140.7 (C), 144.4 (C), 164.6 (C), 177.6 (C). ESMS: m/z 404 (90), 405 (20), 406 (100), 407 (22), 408 (8) (all M+1).

The crude product from the thermal cyclization was a complex mixture and column chromatography (chloroform) gave:

Ethyl 7*H*-7-oxobenzo[*c*]thieno[3,2-*f*]quinazoline-5-carboxylate (14a). This was obtained as a red oil (28%), $R_f = 0.25$, which slowly solidified and had mp 188-190°. ^1H NMR δ 1.41 (t, J = 7.1 Hz, CH_3), 4.41 (q, J = 7.1 Hz, OCH_2), 7.59 (t, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.69 (td, J = 7.3, 1.7 Hz, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 5.6 Hz, 1H), 8.22 (d, J = 8.5 Hz, 1H), 8.32 (s, 1H), 8.49 (dd, J = 7.9, 1.7 Hz, 1H). ^{13}C NMR δ 14.2 (CH_3), 62.1 (OCH_2), 107.6 (CH), 120.1 (CH), 120.8 (CH), 124.1 (C), 126.1 (CH), 126.8 (CH), 128.3 (C), 130.5 (CH), 131.9 (CH), 132.1 (CH), 138.5 (C), 140.8 (C), 143.8 (C), 164.1 (CO), 174.4 (CO). ESMS: m/z 324 (M+1). EIMS (M^+) Found: 323.06302. Calcd for $C_{18}H_{13}NO_3S$: 323.06162.

Benzo[c]thieno[3,2-*f*]quinazolin-7(7*H*)-one (14b). A brown oil (16%), $R_f = 0.18$, which solidified and had mp 185-188°. ^1H NMR δ 6.47 (s, 1H), 6.99 (d, J = 9.3 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 5.5 Hz, 1H), 7.67 (td, J = 7.0, 1.3 Hz, 1H), 7.88 (d, J = 5.5 Hz, 1H), 8.29 (d, J = 8.6 Hz, 1H), 8.53 (dd, J = 7.9, 1.3 Hz, 1H). ^{13}C NMR δ 106.6 (CH), 119.5 (CH), 120.5 (CH), 121.6 (CH), 126.1 (CH), 126.2 (CH), 126.4 (CH), 126.5 (C), 127.9 (CH), 128.9 (C), 130.3 (CH), 137.8 (C), 138.3 (C), 146.0 (C), 174.3 (C). ESMS: m/z 252 (M+1). EIMS (M^+) Found: 251.04132. Calcd for $C_{15}H_9NOS$: 251.04052.

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