Syntheses of 2-hydroxypyrano[3,2-*c*]quinolin-5-ones from 4-hydroxyquinolin-2-ones by tandem Knoevenagel condensation with aldehyde and Michael addition of enamine with the quinone methide—thermo- and photochemical approaches

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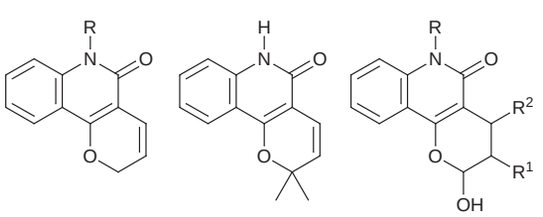
Received (in Cambridge) 6th April 1999, Accepted 27th May 1999

2,3,4,6-Tetrahydro-2-hydroxypyrano[3,2-*c*]quinolin-5-one derivatives **3** are conveniently synthesized from 4-hydroxyquinolin-2(1*H*)-ones **4** by tandem Knoevenagel condensation of **4** with aliphatic aldehyde–Michael-type 1,4-addition of the enamine (derived from the aldehyde and diethylamine *in situ*) with the quinone methide (quinomethane) **9**. This reaction sequence can be achieved in one pot by either direct reaction of **4** with an aldehyde in the presence of diethylamine as a base in refluxing benzene. Alternatively, in the case of **3a**–**c** and **3g** from **4** and acetaldehyde, these syntheses were carried out by way of a photochemical variant by photolysis of a benzene solution of **4** as an electron acceptor and triethylamine as an electron donor, where acetaldehyde and diethylamine are generated *in situ* from triethylamine in redox processes initiated by single-electron transfer (SET) between photoexcited **4** and triethylamine.

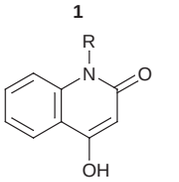
Pyrano[3,2-*c*]quinolin-5-one **1** derivatives constitute a large group of naturally occurring alkaloids represented by, *e.g.*, flindersine **2**.[1] These pyrano[3,2-*c*]quinolin-5-one derivatives and their synthetic analogues are of current research interest not only because they have a wide range of biological activities and therefore have potential medical and other applications,[2] but also because they are often used as synthetic precursors for the preparation of other natural products such as dimeric quinoline alkaloids[3] and other polycyclic heterocycles.[4] Several syntheses of flindersine and benzene-ring-substituted flindersine derivatives have been reported.[5] A couple of 2,3,4,6-tetrahydro-2-hydroxy-2-methylpyrano[3,2-*c*]quinolin-5-ones have been prepared by the reaction of 4-hydroxyquinolin-2(1*H*)-ones **4** with 1-(dimethylamino)butan-3-one in the presence of potassium hydroxide and methyl iodide.[4] Some 6-alkyl-3,4-dihydropyrano[3,2-*c*]quinolin-5-ones were prepared by the reaction of 4-hydroxyquinolin-2(1*H*)-ones **4** with acetylenic halides and the subsequent intramolecular cyclization of the acetylenic ethers.[6] Despite these results, it is obvious that there has so far been no general and convenient method for the syntheses of pyrano-[3,2-*c*]quinolin-5-ones, especially those with different substitution patterns in the pyran ring.

In relation to our interest in using 4-hydroxyquinolin-2(1*H*)-ones for structural elaboration of quinolin-2-ones[7a] and in the photochemistry of quinolinone and isoquinolinone derivatives,[7b–d] we report here a convenient, one-pot synthesis of 2,3,4,6-tetrahydro-2-hydroxypyrano[3,2-*c*]quinolin-5-ones **3** with different alkyl substitutents in the pyran ring, by making use of a heterocyclic quinone methide intermediate[8] generated from Knoevenagel condensation of 4-hydroxyquinolin-2(1*H*)-ones **4** with an aliphatic aldehyde **5**. This then undergoes a Michael-type addition with the *in situ*-formed enamine [from diethylamine (DEA) and the aldehyde], resulting in cyclization and the formation of the pyran ring.



1 **2**

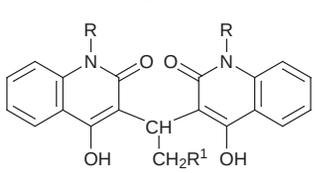
3a R = R^1 = H, R^2 = Me
b R = R^2 = Me, R^1 = H
c R = Et, R^1 = H, R^2 = Me
d R = R^2 = Et, R^1 = Me
e R = R^1 = Et, R^2 = n-Pr
f R = Et, R^1 = n-Pr, R^2 = n-Bu
g R = Ph, R^1 = H, R^2 = Me
h R = Ph, R^1 = Me, R^2 = Et
i R = Et, R^1 = Ph, R^2 = CH_2Ph



4a R = H
b R = Me
c R = Et
d R = Ph

R^1CH_2CHO

5a R^1 = H
b R^1 = Me
c R^1 = Et
d R^1 = n-Pr
e R^1 = Ph



6a R = H, R^1 = H
b R = Me, R^1 = H
c R = Et, R^1 = H
d R = Et, R^1 = Me
e R = Et, R^1 = Et
f R = Et, R^1 = n-Pr
g R = Ph, R^1 = H
h R = Ph, R^1 = Me
i R = Et, R^1 = Ph

Results and discussion

These sequential reactions are achieved in one pot by the reaction of **4** with an aliphatic aldehyde in the presence of DEA as a base. We have also found that, for the syntheses of **3a**–**c** and **3g** (when acetaldehyde was used), these reactions could be carried out using another approach by way of a photoinduced reaction between **4** and triethylamine (TEA), taking advantage of the fact that DEA and acetaldehyde can be generated in photoinduced electron-transfer reactions with TEA as an electron donor.[9]

Table 1 Reactions of quinolin-2-ones **4** with aliphatic aldehydes **5** and DEA[a]

Substrate (mol l^{-1})	Aldehyde (mol l^{-1})	DEA (mol l^{-1})	Reaction time (t/h)	Products and yield (%)[b]
4a (0.01)	**5a** (0.03)	0.03	5	**3a** (51), **6a** (20)
4b (0.05)	**5a** (0.15)	0.15	3	**3b** (60), **6b** (25)
4c (0.05)	**5a** (0.15)	0.15	3	**3c** (50), **6c** (21)
4c (0.05)	**5b** (0.15)	0.15	3	**3d** (74), **6d** (5)
4c (0.05)	**5c** (0.15)	0.15	3	**3e** (60), **6e** (13)
4c (0.05)	**5d** (0.15)	0.15	3	**3f** (75), **6f** (6)
4d (0.05)	**5a** (0.15)	0.15	3	**3g** (43), **6g** (22)
4d (0.05)	**5b** (0.15)	0.15	3	**3h** (89), **6h**[c]
4c (0.05)	**5e** (0.15)	0.15	3	**3i**,[c] **6i** (72)

[a] All the reactions were conducted in refluxing benzene solution. [b] Yield of isolated product. [c] Not obtained.

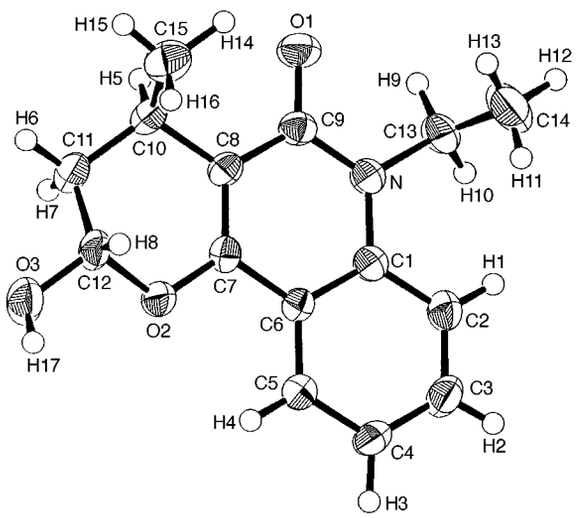


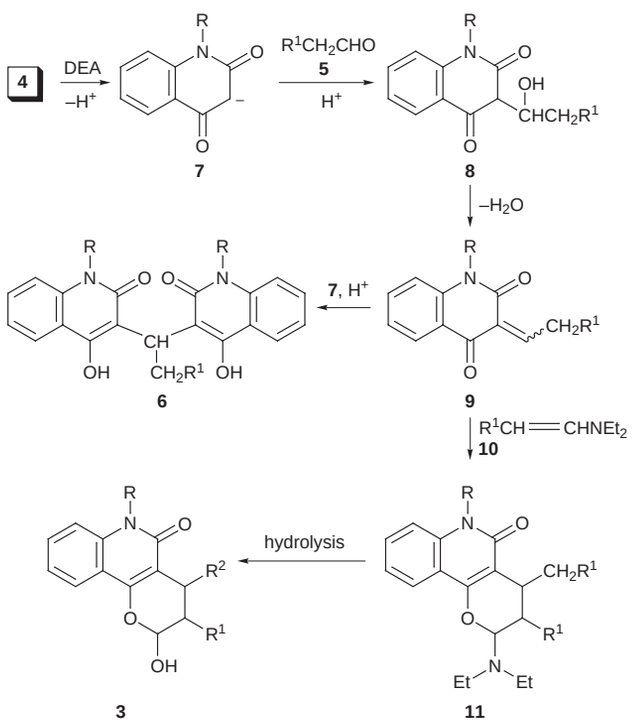
Fig. 1 ORTEP drawing of compound **3c**, with crystallographic numbering scheme.

Direct thermal reactions of 4 with aliphatic aldehydes in the presence of DEA

Refluxing a mixture of **4**, an aldehyde and DEA in benzene solution afforded the corresponding 2,3,4,6-tetrahydropyrano-[3,2-*c*]quinolin-5-one **3** as the main product together with the 3,3′-alkane-1,1-diylbis(4-hydroxyquinolin-2(1*H*)-one) **6** as the minor product. As an example, refluxing **4c** (2.5 mmol), acetaldehyde **5a** (7.5 mmol) and DEA (7.5 mmol) in benzene (83 ml) for 3 h gave product **3c** in 50% yield and **6c** in 21% yield. Product **3c** was isolated as a mixture of two diastereoisomers from column chromatograpy in a ratio of 4 :1 as estimated from the 500 MHz ^{1}H NMR spectrum of the mixture. A pure sample of the major isomer was obtained by recrystallization, and a crystallographic analysis was carried out on this sample which definitely confirmed the structure (Fig. 1). Reactions of the other 4-hydroxyquinolin-2(1*H*)-ones **4a**, **4b** and **4d** with acetaldehyde **5a** gave results similar to **4c** (Table 1), and the tricyclic products **3** were all obtained as mixtures of two stereoisomers in the ratio ≈4 : 1. Reactions of compounds **4** with propionaldehyde **5b**, butyraldehyde **5c** and valeraldehyde **5d** similarly afforded the corresponding tricycles **3** and **6** as products, and compounds **3** were all mixtures of two diastereoisomers with one of them being predominant. However, reaction of **4c** with phenylacetaldehyde **5e** afforded **6i** as the sole product without the formation of the corresponding pyrano[3,2-*c*]quinolin-5-one product **3i**.

In the ^{1}H NMR spectrum of **3c**, the two methylene protons in the NEt group (H9 and H10, following the numbering system in Fig. 1) resonate at δ 4.21 and 4.28, respectively, and partly overlap with each other. An inspection of Fig. 1 and a molecular model of **3c** shows that the free rotation of the N–C13 bond is retarded by the nearby carbonyl and H1, so that the methylene group is fixed in a conformation similar to that in the crystalline state as shown in Fig. 1, with H9 and H10 being situated in different chemical environments. The absorption of the methine proton H5 is at a much lower field (δ 2.98) than the absorption of normal allylic protons ($\delta \approx 1.6$–2) due to the deshielding effect of the nearby carbonyl group. The absorption of H8 is at δ 5.51 with coupling constants of 2.4 and 8.5 Hz with the diastereotopic methylene protons H6 and H7, respectively, while H6 and H7 themselves resonate in the region δ 1.8–1.9. These assignments of the proton absorptions and the coupling patterns are further supported by a two-dimensional H–H COSY spectral measurement on product **3a**.

Two possible mechanisms could account for the formation of product **3** in these reactions. By analogy with reactions of 4-hydroxy-2-pyrone[8h] with aliphatic aldehydes, which yield the corresponding quinone methide, base-catalyzed condensation of a quinolinone **4** with an aldehyde **5** yields the corresponding 4-hydroxy-3-(1-hydroxyethyl)quinolin-2-one **8** (Scheme 1),



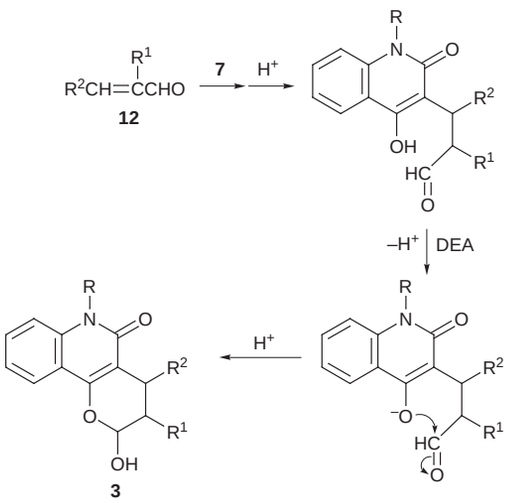
Scheme 1

which is dehydrated on heating in the basic reaction medium to furnish the highly electrophilic quinone methide intermediate **9**. The quinone methide **9** then undergoes competitive Michael addition at the exocyclic methylene carbon by the preformed enamine **10** (from DEA and the aldehyde) and the carbanion **7** derived from the deprotonation of **4**. The Michael-type addition of the enamine proceeds in a 1,4-fashion and results in an intramolecular cyclization to give the 2-(diethylamino)pyrano-[3,2-*c*]quinolin-5-one **11**, which on hydrolysis during the reaction at reflux temperature under the action of a trace amount of water in the reaction mixture, or during work-up on a silica gel column (see Experimental section), affords the final product **3**.† At the same time, addition of the carbanion **7** afforded the alkane-1,1-diylbisquinolone **6**. This mechanism is shown in Scheme 1. The lack of tricyclic product **3i** in the reaction with phenylacetaldehyde is presumably caused by the steric hindrance present both in the enamine (PhCH=CHNEt$_2$) and in the

† Another mechanistic possibility for the formation of **11** is an inverse-electron-demand Diels–Alder reaction between the quinone methide **9** and the enamine **10**.

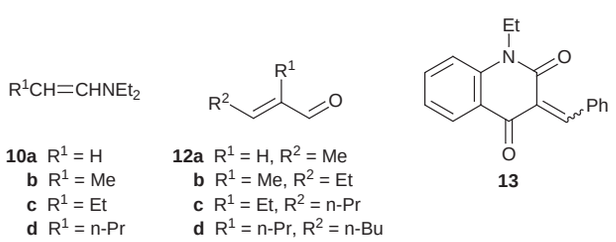
quinone methide intermediate **9** (R′ = Ph) by the introduction of the phenyl substituent.

The formation of product **3** could also be rationalized by a mechanism in which the aldehyde first undergoes an Aldol condensation with itself to give the α,β-unsaturated aldehyde **12**, which subsequently takes part in a Michael addition with the enolate anion of **4** followed by intramolecular cyclization to afford the tricyclic product **3** (Scheme 2). However, this mechanism could not rationalize the formation of product **6**. Furthermore, known reactions of **4** with α,β-unsaturated enals proceeded in a different way with the enal being attacked by the enolate anion **7** at the carbonyl carbon atom instead of the olefinic C3 atom.[5a,e,8f] As an example, reaction of **4** with 3-methylbuten-2-al afforded flindersine **2**.[5a,e] We have further tested this mechanistic possibility under our reaction conditions in a control experiment by refluxing **4** with crotonaldehyde **12a** and DEA in benzene and found that no reaction took place under these conditions.

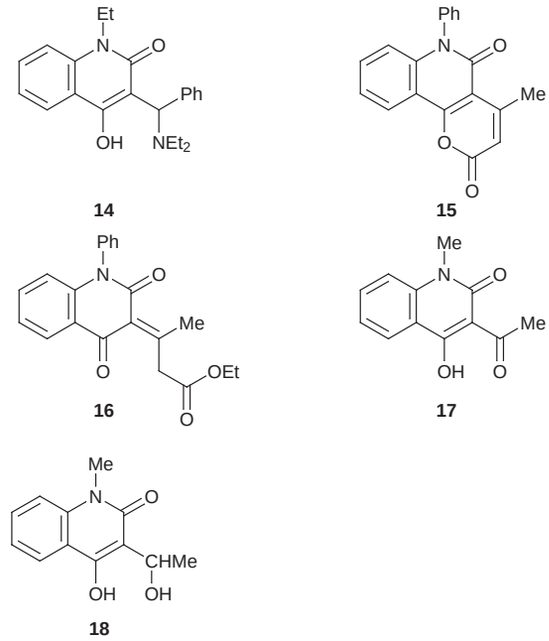


Scheme 2

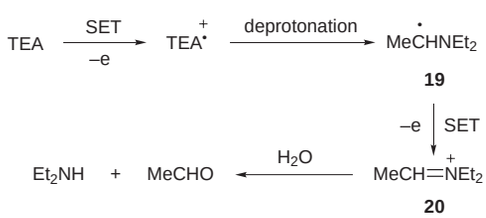
With the aim of further examining the quinone methide mechanism shown in Scheme 1 and exploring the scope of these reactions, the quinone methide **13** was prepared by the condensation of **4** with benzaldehyde in the presence of piperidine as a base, and was then, either *in situ* without separation from the reaction mixture, or separated pure by flash chromatography on a silica gel column, treated with another aldehyde (*e.g.*, acetaldehyde) under reflux with added DEA. It was found that the only product was the amine-trapped product **14**, and no pyrano[3,2-*c*]quinolin-5-one products were formed. This result further helped substantiate the intermediacy of the quinone methide in the above reactions. It also showed that the reactivity of the quinone methide toward different nucleophiles is highly dependent on the substitution pattern at the methylene carbon atom, which modifies the electrophilicity and the steric environment of the quinone methide.



Reaction of **4d** with ethyl acetoacetate in the presence of DEA was also tested. Refluxing a solution of **4d** (2.5 mmol), ethyl acetoacetate (7.5 mmol) and DEA in benzene (83 ml) afforded the 4-methylpyrano[3,2-*c*]quinoline-2,5-dione **15**[10] (15%) and the corresponding bisquinolone (45%). The former is also derived *via* a quinone methide intermediate **16** formed by condensation of **4** with ethyl acetoacetate followed by dehydration. The quinone methide **16**, on deprotonation at the methylene group by DEA, undergoes intramolecular cyclization to furnish **15**.



Additional support of the quinone methide mechanism for the formation of products **3** and **6** came from the result of a photoinduced reaction between 3-acetyl-4-hydroxy-1-methylquinolin-2(1*H*)-one **17** with TEA. It was found that irradiation of a benzene solution of **17** (2.5 mmol) and TEA (7.5 mmol) with light of wavelength longer than 300 nm, where **17** is the only light-absorbing species present, afforded **3b** (42%) as the product. This seemingly unexpected result could be attributed to the photoreduction reaction of **17** as an electron acceptor with TEA as an electron donor. The alcohol **18** is therefore derived from the anion radical of **17**, while acetaldehyde and DEA are derived from the cation radical of TEA by a reaction sequence shown in Scheme 3.[9]



Scheme 3

The alcohol **18** formed in the photoreduction of **17** is dehydrated under the action of the amine as a base (or upon excitation by irradiation‡) at room temperature to give the quinone methide **9**. The quinone methide then took part in a thermal reaction with the acetaldehyde and DEA generated

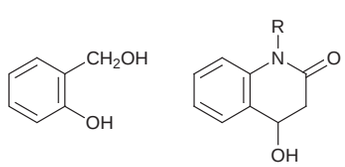
‡ *o*-Hydroxybenzyl alcohol **21** and analogues are known to easily undergo photoinduced dehydration due to the enormously enhanced excited-state acidities as compared with the ground state, caused by a decrease in electron density on the phenolic oxygen atom during the nπ* transition. Therefore, the S_1 state of these compounds has a pK_a-value in the range of 1–4, 6–9 orders of magnitude more acidic than in the ground state.[8g] Although the alcohol **18** includes an *o*-hydroxybenzyl alcohol-like moiety in its structure, the electronic configuration of the excited state of **17** is not clear as yet; it is therefore not certain at the moment whether the irradiation played any role in the room temperature dehydration of **18**.

from $TEA^{+\bullet}$, affording the tricyclic product **3b**. A control experiment showed that **17** could not react with DEA and acetaldehyde even on prolonged reflux in benzene. This excluded the possibility of formation of **3b** by thermal reaction of **17** with DEA and acetaldehyde generated in the photolysis, and provided support for the photoreduction mechanism for the formation of **3b**. It is worth mentioning that although photolytic dehydration of *o*-, *m*- and *p*-hydroxybenzyl alcohols (*e.g.* **21**) has been an established method of generating the corresponding *o*-, *m*- and *p*-quinone methides, respectively,[8e] the sequential transformations of 3-acetyl-4-hydroxyquinolin-2(1*H*)-one **17** to the alcohol **18** in photoreduction and subsequent dehydration of **18** into the quinone methide provided one of the rare examples[8i] of photoinduced generation of a heterocyclic quinone methide. Also, while the mechanistic details of this photoreaction need to be further investigated, the results demonstrated the potential of this reaction sequence as a photochemical method for generating quinone methides from enolized carbocyclic and heterocyclic 1,3-dicarbonyl compounds with an exocyclic acyl group, which merits further exploration.

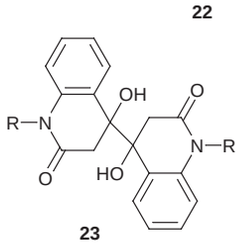
Syntheses of compounds 3 from 4 and *in situ*-photogenerated acetaldehyde and DEA from TEA

Photoinduced cycloaddition reactions of 4-hydroxyquinolin-2-ones **4** with alkenes have been widely investigated and used for the syntheses of furano[3,2-*c*]quinoline and furano[2,3-*b*]-quinoline derivatives.[11] However, photoinduced electron transfer (SET) reactions of **4** with amines have not been reported. Since it is known that acetaldehyde and DEA could be formed in photoinduced SET reactions with TEA as an electron donor by a mechanism shown in Scheme 3, we have examined photoinduced reactions of **4** with TEA and found that these reactions also gave the corresponding tricyclic product **3** and the ethane-1,1-diylbisquinolone **6** in fairly good yields. As an example, photolysis of a solution of **4a** (2.5 mmol) and TEA (7.5 mmol) in benzene (415 ml) with light of wavelength longer than 300 nm for 36 h followed by column chromatographic separation of the reaction mixture furnished **3a** (49%) and **6a** (18%). Photoinduced reactions of **4b**–**d** with TEA in benzene solution gave results similar to **4a** (Table 2). Products **3a**, **3b**, **3c** and **3g** were all obtained as a mixture of two stereoisomers in a ratio of 4 : 1 as shown by their 500 MHz ^{1}H NMR spectra. Photolyses of **4a**–**d** with TEA in acetonitrile also gave results similar to those in benzene.

As can be seen from Scheme 3, the formation of DEA and acetaldehyde from TEA is the consequence of two successive electron transfers to electron acceptors; it is therefore interesting to note that no photoreduction products such as **22** or the



21 **22**



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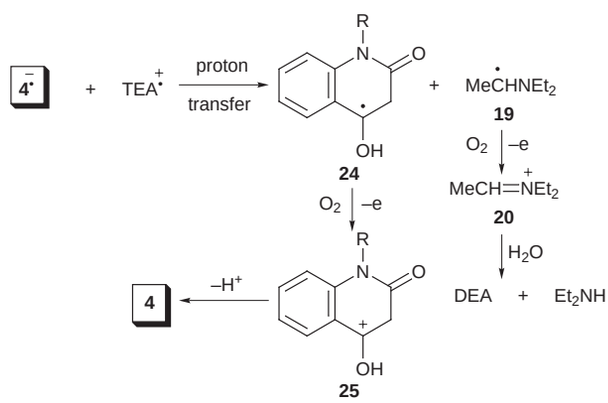
pinacol **23** were isolated in these photoreactions of **4** with TEA, and the total yields of products **3** and **6** based on consumed **4** are rather high. This implies that although the initial SET process in these reactions is certainly that from TEA to photoexcited **4**, since **4** is the only species that has appreciable absorptions in the wavelength region used for the photolysis, the anion radicals of **4** formed in the photo-SET process were not further transformed in any significant extent to reduction products such as **22** and **23**. We therefore speculate that oxygen might be involved in these reactions, serving as an intervening electron acceptor, and a relevant reaction mechanism is formulated in Scheme 4.§

Table 2 Photoinduced reactions of **4** with TEA[a]

Substrate (mol l^{-1})	TEA (mol l^{-1})	Photolysis time (t/h)	Products and yield[b]
4a (0.01)	0.05	36	**3a** (49), **6a** (18)
4b (0.05)	0.25	25	**3b** (61), **6b** (22)
4c (0.05)	0.25	24	**3c** (52), **6c** (20)
4d (0.05)	0.25	28	**3g** (44), **6g** (20)

[a] Reactions were carried out in benzene solution. For details, see Experimental section. [b] Yield of isolated product.



Scheme 4

This mechanism is also supported by the following thermodynamic considerations. The half-wave reduction potential ($E^{red}_{1/2}$) of oxygen is −0.38 V [MeCN, standard calomel electrode (SCE),[12] while the half-wave oxidation potential ($E^{ox}_{1/2}$) of the α-aminoalkyl radical MeĊHNEt$_2$ is −1.12 V (MeCN, SCE).[13] The $E^{ox}_{1/2}$ of the α-hydroxyalkyl radical **19** is not known, but should be close to that of the Me$_2$ĊOH radical ($E^{ox}_{1/2}$ −0.70 V, SCE).[13] As a result, single-electron-transfer processes from these radicals to ground-state oxygen are exothermic [0.32 eV (7.4 kcal mol^{-1}¶) and 0.74 eV (17 kcal mol^{-1}), respectively] and are therefore thermodynamically feasible. The oxidation of radical **24** afforded the α-hydroxyalkyl carbocation **25**, which on deprotonation regenerated **4**, and oxidation of the α-aminoalkyl radical **19** yielded the iminium salt **20**, which was hydrolyzed under the action of a trace amount of water in the solvent to give acetaldehyde and DEA.

Therefore, **4** is actually not significantly consumed in photoreductions, but is mainly converted to the tricyclic product **3** and the bisquinolone **6** in subsequent thermal reactions with MeCHO and DEA generated in the photoreactions *via* a quinone methide intermediate, which was again formed by dehydration of the alcohol **8** (Scheme 1).

In summary, convenient and efficient one-pot syntheses of 2,3,4,6-tetrahydro-2-hydroxypyrano[3,2-*c*]quinolin-5-one

§ The photolyses were carried out with continuous bubbling of a stream of dry argon which is known to contain a trace amount of oxygen. The oxygen brought into the solution by the argon gas stream will suffice to effect the oxidations denoted in Scheme 4, considering the long irradiation time.

¶ 1 cal = 4.184 J.

derivatives from simple starting materials have been developed by way of a quinone methide intermediate. This tandem Knoevenagel condensation of **4** with an aldehyde and Michael-type 1,4-addition of the preformed **12** (from the aldehyde and DEA) to the quinone methide **9** can be achieved either by direct reaction of **4** with an aliphatic aldehyde in the presence of DEA as a base, or, in the case of reactions of **4** with acetaldehyde for the syntheses of **3a**–**c** and **3g**, by a photochemical approach in which acetaldehyde and DEA are conveniently generated *in situ* from photoinduced redox processes initiated by SET between photoexcited **4** and TEA.

Extensions and modifications of the generation and reactions of the quinone methide intermediate **9** and the scope and mechanistic details of the photochemical variant of these reactions are to be further explored.

Experimental

Mps were measured on a YANACO microscopic melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL PMX-60 SI spectrometer at 60 MHz or on a Bruker AC-500 spectrometer at 500 MHz with $SiMe_4$ as internal standard and $CDCl_3$ as solvent unless otherwise stated. *J* Values are given in Hz. IR spectra were taken with a Shimadzu IR 408 or a Nicolet 5DX FT-IR spectrometer for samples in KBr pellets. Mass spectra were recorded with a VG ZAB-HS spectrometer. Elemental analyses were obtained using a Perken-Elmer 240 C analyzer.

4-Hydroxyquinolin-2-ones **4** were prepared in 70–80% yields according to the literature procedures;[14a] 3-acetyl-4-hydroxyquinolin-2(1*H*)-one was prepared by the reported method.[14b] Acetonitrile (AR grade) was first refluxed with phosphorus pentaoxide and distilled, then refluxed with anhydrous potassium carbonate and distilled. Benzene (AR grade) was dried with sodium and distilled before use. DEA and TEA (AR grade) were dried with potassium hydroxide and distilled before use. Acetaldehyde was extracted from an aqueous solution (40%) with benzene, and the benzene solution was dried with $CaCl_2$. The other aldehydes were distilled under nitrogen before use. All the other reagents were CP or AR grade and were used as received without further purification. Petroleum spirit refers to the fraction with distillation range 60–90 °C.

General procedures for the preparation of 3 and 6

(a) Thermal reactions. The corresponding compound **4** (2.5 mmol) was dissolved in benzene (83 ml), DEA (7.5 mmol) was then added, and the mixture was refluxed for the time indicated in Table 1. The reaction course was monitored by TLC. At the end of the reaction, the solvent was removed *in vacuo* and the residue was subjected to silica gel column chromatography with petroleum spirit–ethyl acetate as eluent for gradient elution to afford the products **3** and **6**.

(b) Photochemical reactions. All the photolyses were carried out with light of wavelength longer than 300 nm from a 500 W medium-pressure mercury lamp in a glass cooling water-jacket. The photolysate was placed in glass tubes around the light source to be photolyzed. A stream of argon was bubbled through the solution during photolyses for agitation.

*Photolysis of **4** with TEA in benzene solution.*—A solution of compound **4** (2.5 mmol) and TEA (7.5 mmol) in benzene (83 ml) was irradiated for the time indicated in Table 2. The reaction course was monitored by TLC. At the end of the reaction, the solvent was removed *in vacuo* and the residue was subjected to silica gel column chromatography with petroleum spirit–ethyl acetate as eluent for gradient elution to afford the products **3** and **6**.

*Photolysis of 3-acetyl-4-hydroxyquinolin-2(1H)-one **17** with TEA in benzene solution.*—A solution of **17** (533 mg, 2.5 mmol) and TEA (758 mg, 7.5 mmol) in benzene (83 ml) was photolyzed for 28 h. TLC monitoring of the reaction indicated the complete consumption of **17**. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column with petroleum spirit–ethyl acetate as eluent to afford **3b** (270 mg, 42%).

2,3,4,6-Tetrahydro-2-hydroxy-4-methylpyrano[3,2-*c*]quinolin-5-one 3a. *Colorless prisms*, mp 146–148 °C (from petroleum spirit–ethyl acetate) (Found: C, 67.99; H, 5.58; N, 6.26. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%); ν_{max}/cm^{-1} 3300 (OH), 1642, 1610, 1120, 839, 776; δ_H (500 MHz; DMSO-d_6; H–H COSY) 11.39 (1H, s, NH), 7.27–7.80 (3H, m, ArH), 7.14 (1H, t, *J* 8.7, ArH), 5.53 (1H, dd, *J* 2 and 8.5, CH), 2.97 (1H, dd, *J* 6.6 and 9.5, CH), 1.81–1.93 (2H, m, CH_2), 1.25 (3H, d, *J* 6.6, CH_3); *m*/*z* (EI) 231 (M^+, 73%), 216 (14), 202 (86), 188 (100), 175 (41), 161 (19), 130 (13), 120 (28), 77 (9).

2,3,4,6-Tetrahydro-2-hydroxy-4,6-dimethylpyrano[3,2-*c*]quinolin-5-one 3b. *Colorless prisms*, mp 193–195 °C (from petroleum spirit–ethyl acetate), (Found: C, 68.49; H, 6.02; N, 5.23%. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71%); ν_{max}/cm^{-1} 3230 (OH), 1635, 1612, 1588, 1150, 825, 770; δ_H (500 MHz) 7.33–7.80 (3H, m, ArH), 7.23 (1H, t, *J* 9.0, ArH), 5.51 (1H, dd, *J* 2.8 and 8.3, CH), 3.60 (3H, s, NCH_3), 3.00 (1H, m, CH), 1.84–1.92 (2H, m, CH_2), 1.25 (3H, d, *J* 6.7, CH_3); *m*/*z* (EI) 245 (M^+, 89%), 230 (17), 216 (92), 202 (100), 175 (18), 134 (23), 77 (29).

6-Ethyl-2,3,4,6-tetrahydro-2-hydroxy-4-methylpyrano[3,2-*c*]-quinolin-5-one 3c. *Colorless prisms*, mp 229–231 °C (from petroleum spirit–ethyl acetate) (Found: C, 69.50; H, 6.56; N, 5.40%. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40%); ν_{max}/cm^{-1} 3200 (OH), 1628, 1608, 1580, 1150, 982, 836, 764; δ_H (500 MHz, DMSO-d_6) 7.37–7.90 (3H, m, ArH), 7.20 (1H, t, *J* 9.1, ArH), 5.51 (1H, dd, *J* 2.4 and 8.5, CH), 4.21 (1H, m, 1/2 × CH_2), 4.28 (1H, m, 1/2 × CH_2), 2.98 (1H, dd, *J* 5.5 and 8.5, CH), 1.81–1.91 (2H, m, CH_2), 1.29 (3H, d, *J* 8.5, CH_3), 1.20 (3H, t, *J* 8.3, CH_3); *m*/*z* (EI) 259 (M^+, 100%), 244 (M − Me, 18), 230 (M − CH_2CH_3, 94), 216 (72), 202 (22), 188 (23), 161 (11), 146 (13), 132 (14), 77 (10).

4,6-Diethyl-2,3,4,6-tetrahydro-2-hydroxy-3-methylpyrano-[3,2-*c*]quinolin-5-one 3d. *Colorless prisms*, mp 190–192 °C (from petroleum spirit–ethyl acetate) (Found: C, 71.42; H, 7.43; N, 5.04%. $C_{17}H_{21}NO_3$ requires C, 71.06; H, 7.36; N, 4.87%) ν_{max}/cm^{-1} 3250 (OH), 1630, 1610, 1160, 850, 762; δ_H (60 MHz) 7.01–8.10 (4H, m, ArH), 5.50 (1H, d, *J* 2.8, CH), 4.37 (2H, q, *J* 7.0, CH_2), 3.59 (1H, br, OH), 2.67 (1H, m, CH), 2.21 (1H, m, ½ × CH_2), 1.37 (1H, m, ½ × CH_2), 1.35 (3H, t, *J* 7.0, CH_3), 1.05 (3H, dd, *J* 2.0 and 7.0, CH_3), 0.98 (3H, d, *J* 6.0, CH_3); *m*/*z* (EI) 287 (M^+, 31%), 258 (M − CH_2CH_3, 59), 230 (100), 214 (81), 186 (31), 174 (11), 146 (15), 132 (15), 77 (18).

3,6-Diethyl-2,3,4,6-tetrahydro-2-hydroxy-4-propylpyrano-[3,2-*c*]quinolin-5-one 3e. *Colorless prisms*, mp 142–144 °C (from petroleum spirit–ethyl acetate) (Found: C, 72.90; H, 7.69; N, 4.53%. $C_{19}H_{25}NO_3$ requires C, 72.35; H, 7.99; N, 4.44%); ν_{max}/cm^{-1} 3300 (OH), 1628, 1608, 1160, 760; δ_H (60 MHz) 6.83–8.10 (4H, m, ArH), 5.63 (1H, d, *J* 2.0, CH), 4.40 (2H, q, *J* 7.8, CH_2), 4.24 (1H, br, OH), 2.87 (1H, m, CH), 1.51–2.33 (7H, m, CH_2CH_2 and $CHCH_2$), 1.35 (3H, t, *J* 7.2, CH_3), 0.76–1.20 (6H, m, 2 × CH_3); *m*/*z* (EI) 315 (M^+, 13%), 286 (M − CH_2CH_3, 9), 273 (61), 258 (9), 244 (87), 214 (100), 202 (49), 174 (15), 146 (15), 132 (14), 77 (15).

4-Butyl-6-ethyl-2,3,4,6-tetrahydro-2-hydroxy-3-propyl-2*H*-pyrano[3,2-*c*]quinolin-5-one 3f. *Colorless prisms*, mp 137–139 °C (from petroleum spirit–ethyl acetate) (Found: C, 73.68; H, 8.75; N, 3.89%. $C_{21}H_{29}NO_3$ requires C, 73.44; H, 8.51; N, 4.08%); ν_{max}/cm^{-1} 3200 (OH), 1620, 1600, 1580, 1150, 750; δ_H (60

MHz) 6.90–8.10 (4H, m, ArH), 5.62 (1H, d, *J* 2.8, CH), 4.30 (2H, q, *J* 7.2, CH_2), 4.03 (1H, br, OH), 3.05 (1H, m, CH), 1.50–2.10 (11H, m, $CHCH_2CH_2$ and $CH_2CH_2CH_2$), 1.42 (3H, t, *J* 7.2, CH_3), 0.90–1.10 (6H, m, 2 × CH_3); *m*/*z* (EI) 343 (M^+, 24%), 314 (M − CH_2CH_3, 13), 300 (12), 287 (76), 258 (80), 244 (53), 214 (85), 202 (100), 174 (21), 146 (16), 132 (14), 77 (15).

2,3,4,6-Tetrahydro-2-hydroxy-4-methyl-6-phenylpyrano-[3,2-*c*]quinolin-5-one 3g. *Colorless prisms*, mp 224–226 °C (from petroleum spirit–ethyl acetate) (Found: C, 73.88; H, 5.45; N, 4.86%. $C_{19}H_{17}NO_3$ requires C, 74.25; H, 5.65; N, 4.56%); ν_{max}/cm^{-1} 3200 (OH), 1630, 1595, 1160, 760, 710; δ_H (500 MHz) 7.25–7.98 (7H, m, ArH), 7.14 (1H, t, *J* 8.9, ArH), 6.61 (1H, d, *J* 10.0, ArH), 5.56 (1H, d, *J* 8.4, CH), 3.48 (1H, br, OH), 3.18 (1H, m, CH), 1.91–2.05 (2H, m, CH_2), 1.33 (3H, d, *J* 6.5, CH_3); *m*/*z* (EI) 307 (M^+, 100%), 289 (M − H_2O, 10), 279 (M − CO, 33), 274 (48), 262 (49), 251 (38), 237 (13), 195 (16), 167 (18), 77 (13).

4-Ethyl-2,3,4,6-tetrahydro-2-hydroxy-3-methyl-6-phenyl-pyrano[3,2-*c*]quinolin-5-one 3h. *Colorless prisms*, mp 177–179 °C (from petroleum spirit–ethyl acetate) (Found: C, 75.58; H, 6.46; N, 4.01%. $C_{21}H_{21}NO_3$ requires C, 75.20; H, 6.31; N, 4.18%); ν_{max}/cm^{-1} 3300 (OH), 1610, 1585, 1560, 1170, 760, 700; δ_H (60 MHz) 6.50–8.20 (9H, m, ArH), 5.52 (1H, d, *J* 5.8, CH), 3.50 (1H, br, OH), 2.60 (1H, m, CH), 2.10 (1H, m, CH), 0.90–1.35 (8H, m, CH_3 and CH_2CH_3); *m*/*z* (EI) 335 (M^+, 33%), 306 (M − CH_2CH_3, 45), 292 (13), 278 (100), 262 (79), 204 (14), 167 (17), 139 (6), 77 (12).

4,4′-Dihydroxy-3,3′-(ethane-1,1-diyl)diquinolin-2(1*H*)-one 6a. *Colorless prisms*, mp 295–297 °C (from acetone–ethyl acetate) (Found: C, 69.27; H, 4.42; N, 8.46%. $C_{20}H_{16}N_2O_4$ requires C, 68.96; H, 4.63; N, 8.04%); ν_{max}/cm^{-1} 2520br, 1650, 1602, 1390, 748; δ_H (60 MHz) 13.50 (2H, br, 2 × OH), 11.95 (2H, s, 2 × NH), 7.00–7.92 (8H, m, ArH), 4.85 (1H, q, *J* 7.1, CH), 1.80 (3H, d, *J* 7.1, CH_3); *m*/*z* (FAB) 349 (M^+ + 1, 26%), 319 (3), 217 (33), 108 (12), 91 (58), 90 (49), 77 (45), 57 (100).

4,4′-Dihydroxy-1,1′-dimethyl-3,3′-(ethane-1,1-diyl)diquinolin-2(1*H*)-one 6b. *Colorless needles*, mp 265–267 °C (from ethyl acetate) (Found: C, 70.40; H, 5.14; N, 7.21%. $C_{22}H_{20}N_2O_4$ requires C, 70.20; H, 5.36; N, 7.44%); ν_{max}/cm^{-1} 2550br, 1630, 1600, 1542, 760; δ_H (60 MHz) 12.10 (2H, br, 2 × OH), 7.15–8.33 (8H, m, ArH), 5.09 (1H, q, *J* 7.2, CH), 3.72 (6H, s, 2 × CH_3), 1.86 (3H, d, *J* 7.2, CH_3); *m*/*z* (EI) 376 (M^+, 20%), 361 (M − Me, 4), 227 (7), 212 (24), 200 (63), 175 (100), 132 (36), 104 (42), 77 (44).

1,1′-Diethyl-4,4′-dihydroxy-3,3′-(ethane-1,1-diyl)diquinolin-2(1*H*)-one 6c. *Colorless needles*, mp 279–281 °C (from ethyl acetate) (Found: C, 71.50; H, 6.02; N, 6.49%. $C_{24}H_{24}N_2O_4$ requires C, 71.27; H, 5.98; N, 6.93%); ν_{max}/cm^{-1} 2550br, 1625, 1600, 1540, 758, 700; δ_H (60 MHz) 13.05 (2H, br, 2 × OH), 7.10–8.46 (8H, m, ArH), 5.08 (1H, q, *J* 7.0, CH), 4.43 (4H, q, *J* 7.2, 2 × CH_2), 1.93 (3H, d, *J* 7.0, CH_3), 1.41 (6H, t, *J* 7.2, 2 × CH_3); *m*/*z* (EI) 404 (M^+, 23%), 215 (94), 203 (28), 188 (100), 172 (39), 161 (49), 132 (85), 119 (28), 104 (26), 77 (76).

1,1′-Diethyl-4,4′-dihydroxy-3,3′-(propane-1,1-diyl)diquinolin-2(1*H*)-one 6d. *Colorless needles*, mp 248–250 °C (from ethyl acetate) (Found: C, 71.58; H, 6.36; N, 6.31%. $C_{25}H_{26}N_2O_4$ requires C, 71.75; H, 6.26; N, 6.70%); ν_{max}/cm^{-1} 2520br, 1625, 1600, 1540, 760; δ_H (60 MHz) 13.00 (2H, br, 2 × OH), 7.00–8.27 (8H, m, ArH), 4.63 (1H, t, *J* 8.2, CH), 4.37 (4H, q, *J* 7.0, 2 × CH_2), 2.20–2.70 (2H, m, CH_2), 1.37 (6H, t, *J* 7.0, 2 × CH_3), 0.91 (3H, t, *J* 7.2, CH_3); *m*/*z* (EI) 418 (M^+, 68%), 403 (M − CH_3, 56), 389 (57), 268 (52), 229 (41), 214 (100), 203 (82), 189 (42), 161 (31), 132 (39), 77 (34).

1,1′-Diethyl-4,4′-dihydroxy-3,3′-(butane-1,1-diyl)diquinolin-2(1*H*)-one 6e. *Colorless needles*, mp 172–174 °C (from ethyl acetate) (Found: C, 72.50; H, 6.87; N, 6.28%. $C_{26}H_{28}N_2O_4$ requires C, 72.20; H, 6.53; N, 6.48%); ν_{max}/cm^{-1} 2500br, 1626, 1600, 1540, 760; δ_H (60 MHz) 13.10 (2H, br, 2 × OH), 7.00–8.27 (8H, m, ArH), 4.76 (1H, t, *J* 8.0, CH), 4.31 (4H, q, *J* 7.2, 2 × CH_2), 2.20–2.55 (2H, m, CH_2), 1.30 (6H, t, *J* 7.2, 2 × CH_3), 0.68–1.12 (5H, m, CH_2CH_3); *m*/*z* (EI) 432 (M^+, 16%), 403 (M − CH_2CH_3, 30), 389 (11), 268 (11), 243 (30), 214 (100), 203 (19), 189 (35), 161 (27), 146 (26), 132 (31), 77 (25).

1,1′-Diethyl-4,4′-dihydroxy-3,3′-(pentane-1,1-diyl)diquinolin-2(1*H*)-one 6f. *Colorless needles*, mp 116–118 °C (from ethyl acetate) (Found: C, 72.32; H, 6.99; N, 6.37%. $C_{27}H_{30}N_2O_4$ requires C, 72.62; H, 6.77; N, 6.27%); ν_{max}/cm^{-1} 2555br, 1625, 1605, 1546, 760; δ_H (60 MHz) 13.05 (2H, br, 2 × OH), 7.00–8.30 (8H, m, ArH), 4.77 (1H, t, *J* 8.0, CH), 4.38 (4H, q, *J* 7.4, 2 × CH_2), 2.38 (2H, m, CH_2), 0.67–1.63 (13H, m, 3 × CH_3 and CH_2CH_2); *m*/*z* (EI) 446 (M^+, 18%), 403 (M − CH_2CH_2-CH_3, 25), 257 (39), 228 (17), 214 (100), 189 (43), 161 (38), 146 (31), 132 (38), 77 (29).

4,4′-Dihydroxy-1,1′-diphenyl-3,3′-(ethane-1,1-diyl)diquinolin-2(1*H*)-one 6g. *Colorless needles*, mp 285–287 °C (from acetone–ethyl acetate) (Found: C, 76.82; H, 4.91; N, 5.36%. $C_{32}H_{24}N_2O_4$ requires C, 76.79; H, 4.83; N, 5.60%); ν_{max}/cm^{-1} 2550br, 1620, 1608, 1542, 760, 712; δ_H (500 MHz) 13.09 (1H, br, OH), 12.20 (1H, br, OH), 8.15 (2H, t, *J* 9.5, ArH), 7.53–7.65 (6H, m, ArH), 7.38 (2H, d, *J* 9.1, ArH), 7.32 (2H, t, *J* 9.3, ArH), 7.22 (4H, t, *J* 9.1, ArH), 6.63 (2H, t, *J* 9.9, ArH), 5.08 (1H, q, *J* 7.2, CH), 1.95 (3H, d, *J* 7.2, CH_3); *m*/*z* (EI) 500 (M^+, 2%), 317 (1), 288 (2), 262 (99), 237 (78), 195 (100), 167 (54), 139 (14), 77 (42).

1,1′-Diethyl-4,4′-dihydroxy-3,3′-(2-phenylethane-1,1-diyl)-diquinolin-2(1*H*)-one 6i. *Colorless needles*, mp 217–219 °C (from ethyl acetate) (Found: C, 75.11; H, 5.38; N, 6.15%. $C_{30}H_{28}N_2O_4$ requires C, 74.98; H, 5.87; N, 5.83%); ν_{max}/cm^{-1} 2500br, 1625, 1605, 1540, 765, 705; δ_H (60 MHz) 12.01 (2H, br, 2 × OH), 6.90–8.37 (13H, m, ArH), 5.17 (1H, t, *J* 8.0, CH), 3.50–4.67 (4H, m, 2 × CH_2), 1.10–1.60 (8H, m, 2 × CH_3 and CH_2); *m*/*z* (EI) 480 (M^+, 14%), 389 (M − CH_2Ph, 100), 291 (40), 268 (55), 214 (21), 189 (26), 146 (25), 130 (27), 77 (24).

3-[α-(Diethylamino)benzyl]-1-ethyl-4-hydroxyquinolin-2(1*H*)-one 14. *Colorless prisms*, mp 139–141 °C (decomp.) (from ethyl acetate) (Found: C, 75.57; H, 7.38; N, 7.65%. $C_{22}H_{26}N_2O_2$ requires C, 75.40; H, 7.48; N, 7.99%); ν_{max}/cm^{-1} 3230, 1638, 1605, 1582, 908, 820, 760; δ_H (500 MHz, DMSO-d_6) 13.00 (1H, br, OH), 7.00–8.30 (9H, m, ArH), 6.37 (1H, s, CH), 4.31–4.47 (4H, m, 2 × CH_2), 2.93 (2H, q, *J* 7.2, CH_2), 1.40 (3H, t, *J* 7.2, CH_3), 1.29–1.34 (6H, m, 2 × CH_3); *m*/*z* (EI) 350 (M^+, 0.03%), 276 (19), 248 (9), 189 (19), 161 (16), 147 (14) 132 (25), 77 (22), 58 (100).

4-Methyl-6-phenylpyrano[3,2-*c*]quinoline-2,5(6*H*)-dione 15. *Yellow needles*, mp 270–272 °C (from petroleum spirit–ethyl acetate) (Found: C, 75.62; H, 4.18; N, 4.80%. Calc. for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62%); ν_{max}/cm^{-1} 1732, 1650, 1600, 1580, 1450, 1092, 765, 705; δ_H (500 MHz) 8.30 (1H, d, *J* 9.3, ArH), 7.62 (2H, t, *J* 9.3, ArH), 7.55 (1H, d, *J* 8.7, ArH), 7.43 (1H, t, *J* 9.3, ArH), 7.25–7.30 (3H, m, ArH), 6.39 (1H, d, *J* 10.1, ArH), 6.21 (1H, s, =CH–), 2.67 (3H, s, CH_3); *m*/*z* (EI) 303 (M^+, 80%), 275 (M − CO, 100), 246 (45), 217 (11), 167 (18), 77 (22).

Crystal structure of 3c

$C_{15}H_{17}NO_3$, M = 259.30. Triclinic, space group $P\bar{1}$(#2) with a = 9.405(3), b = 9.677(4), c = 8.158(4) Å, α = 107.91(4)°, β = 100.72(3)°, γ = 106.76(3)°, V = 645.0(5) $Å^3$, Z = 2, D_c = 1.335 g

cm^{-3}. Absorption coefficient 0.930 mm^{-1}, $F(000) = 276.00$. A colorless prismatic crystal of 0.20 × 0.20 × 0.30 mm was used. Data were collected on a Rigaku AFC7R diffractometer equipped with graphite-monochromated Mo-Kα radiation using the ω–2θ scan technique to a maximum 2θ-value of 50.0°. The structure was solved by a direct method (MITHRIL84) and refined by full-matrix least-squares. A total of 2433 independent reflections [R(int) = 0.034] were used in the refinement which converged with $R = 0.048$ and $Rw = 0.050$.

CCDC reference number 207/336. See http://www.rsc.org/suppdata/p1/1999/2017 for crystallographic files in .cif format.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (29772016) and the Natural Science Foundation of Jiangsu Province (BK97017).

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