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Depending on the ester substituent, diethyl 2-(3-nitro-2-oxo-4-quinolinyl)malonates **2** give upon thermolysis ethyl 2-(3-nitro-2-oxo-4-quinolinyl)acetates **4**, whereas dimethyl 2-(3-nitro-2-oxo-4-quinolinyl)-malonates **3** cyclize to give 1-methoxycarbonylisoxazolo[3,4-*c*]quinolin-4(5*H*)-ones **5**. The necessary reaction conditions can be obtained easily with the help of differential scanning calorimetry.

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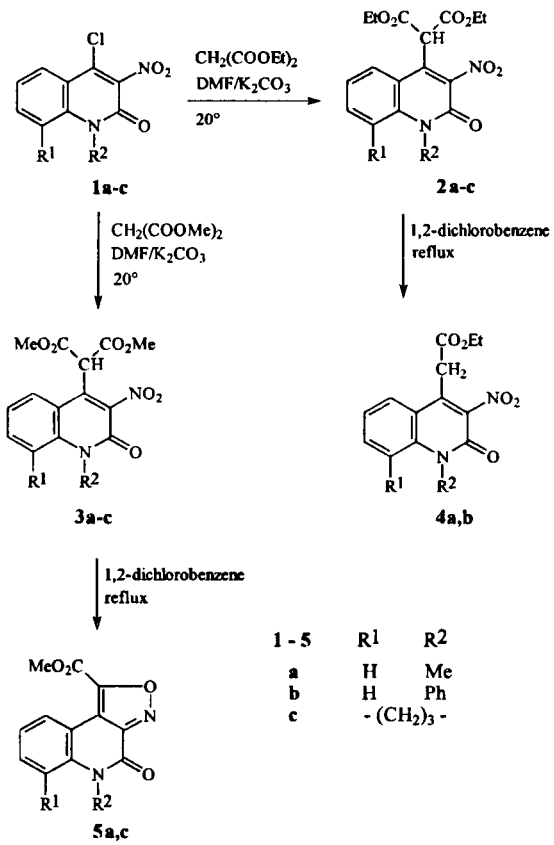
Recently we started a series of experiments in order to investigate the usefulness of differential scanning calorimetry in synthetic organic chemistry [1]. This thermoanalytic method which is widely used in material science, quality inspection, polymer and biopolymer chemistry and pharmacy [2], provides useful informations and hints for organic synthesis in the stage of planning thermolytical reactions such as ring closure and rearrangement reactions. During our investigation for a new approach to derivatives of 2-oxo-4-quinolinylacetates, a compound class which is known to have interesting pharmacological activity [3,4], we found that reactive 1-chloro-3-oxo-hetarenes and analogous carbocyclic derivatives react with active methylene compounds by nucleophilic substitution of the chlorine atom by a carbanion group. In this manner 4-chloro-3-nitro-2-quinolones **1a-c** reacted with diethyl or dimethyl malonates in the presence of potassium carbonate already at room temperature to give 2-(3-nitro-2-oxo-4-quinolinyl)malonates **2a-c** and **3a-c**, respectively.

Scheme 1



When we investigated the thermal behaviour of 2-(3-nitro-2-oxo-4-quinolinyl)malonates **2** having an ethyl ester moiety by differential scanning calorimetry, this analytical method showed that an exothermic reaction (ΔH between -48 and -78 mcal/mg) started in the region of 150-170° (Figure 1). We carried out this reaction in a preparative manner by thermolysis of the diethyl malonates **2** in refluxing bromobenzene and obtained in excellent yields a new product, which could be shown to be ethyl 2-(3-nitro-2-oxo-4-quinolinyl)-acetates **4**. Thus this reaction sequence offers a new and convenient route to 2-oxo-4-quinolinylacetates.

The formation of **4** can be explained easily by the elimination of ethene from the ethyl ester moiety and subsequent decarboxylation of the free malonic acid group, a reaction mechanism, which was observed similary in the thermolysis of acyl malonates during gas chromatographic analyses [5]. The formation of gaseous reaction products can be observed in the melting point apparatus and also during the calorimetric analysis, because the lids of standard pans were opened by the pressure and caused poor differential scanning calorimetry plots and forced us to use sealed crucibles.

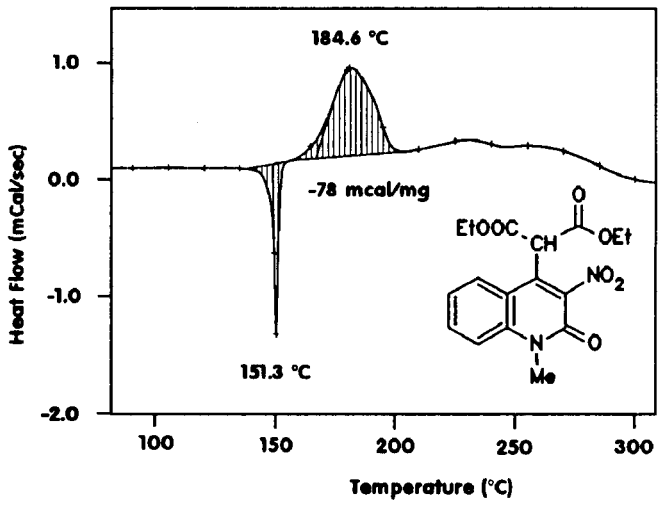


Figure 1. Differential scanning calorimetry-plot of **2a**.

The calorimetric analysis of the 2-(3-nitro-2-oxo-4-quinolinyl)malonates **3** with a methyl ester moiety indicated again that an exothermic thermolytic reaction in the region of 150-180° started (Figure 2), but with slightly higher reaction enthalpies (ΔH between -65 and -90 mcal/mg). Surprisingly, when we studied this reaction in a preparative manner by heating **3** in refluxing 1,2-dichlorobenzene, we did not obtain methyl acetates analogous to **4**, but we isolated cyclization products, namely 1-methoxycarbonylisoxazolo[3,4-*c*]-quinolin-4(5*H*)-ones **5**, as could be seen from spectroscopic and analytical data. This reaction sequence of **3** to **5** offers a new and interesting route to functionalized isoxazoles.

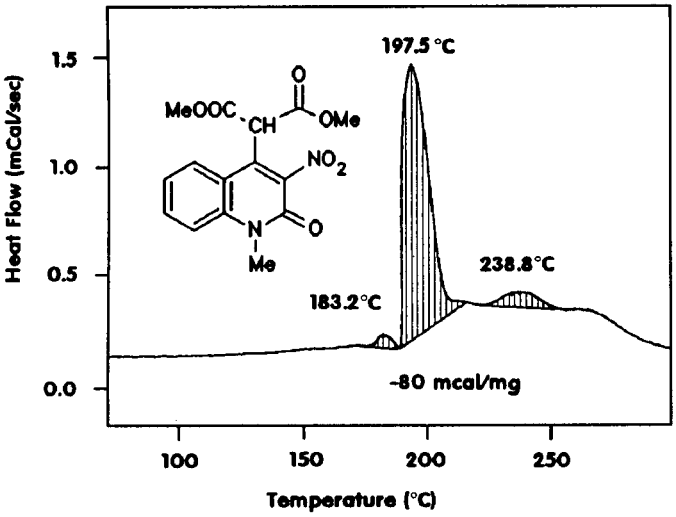


Figure 2. Differential scanning calorimetry-plot of **3a**.

The reason why the methyl esters did not form acetates **4**, seems to be the impossibility of the primary formation of ethene. The mechanism of formation of **5** involves the loss of carbon dioxide and methanol, probably initiated by a transfer of the methyl group to the nitro group, followed by the cyclization to the isoxazolo ring. Also during the decomposition of **3** a gas evolution in the melting point apparatus and during the differential scanning calorimetry analysis (in standard pans) can be observed.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Model MFB-595 in open capillary tubes. Calorimetric data were obtained on a Rheometric Scientific DSC-Plus instrument with the differential scanning calorimetry software V5.42. The differential scanning calorimetry plots were recorded between 25-400°, with a heating rate of 2-10°/minute, and 1.5-3 mg of compound in sealed aluminium crucibles (11 bar). The ^{1}H nmr spectra were recorded on a Varian Gemini 200 instrument (200 MHz) or a Bruker AM 360 instrument (360 MHz). The ^{13}C nmr-spectra were recorded on a Bruker AM 360 instrument (90 MHz). The solvent for nmr spectra was deuteriodimethyl sulfoxide unless otherwise stated. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer or a Galaxy Series FTIR 7000 in potassium bromide pellets. Elemental analyses were performed on a Fisons elemental analyzer, Model EA 1108 and are within ±0.4 of the theoretical percentages. All reactions were monitored by thin layer chromatography carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

4-Chloro-1-methyl-3-nitro-2(1*H*)-quinolone (**1a**), 4-Chloro-3-nitro-1-phenyl-2(1*H*)-quinolone (**1b**) and 1-Chloro-2-nitro-6,7-dihydro-5*H*-benzo[*i,j*]quinolizin-3-one (**1c**).

Syntheses were performed according to ref [6].

Diethyl 2-(1-Methyl-3-nitro-2-oxo-1,2-dihydroquinolin-4-yl)-malonate (**2a**).

A mixture of **1a** (2.39 g, 10 mmoles), diethyl malonate (3.20 g, 20 mmoles) and anhydrous potassium carbonate (3.0 g) in dimethyl formamide (40 ml) was stirred at room temperature for 5 hours. After dilution with ice/water (200 ml) the solution was slowly acidified with concentrated hydrochloric acid to *p*H = 1 to precipitate the product. After standing for about 12 hours the precipitate was filtered by suction and washed with water, the yield was 3.40 g (94%), pale yellow prisms, mp 151° (ethanol); calorimetric data for thermolysis: onset 169.1°, peak 184.6°, ΔH -78 mcal/mg; ir: 1740 s, 1660 s cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.20 (t, J = 6 Hz, 2 ethyl-CH_3), 3.75 (s, NCH_3), 4.25 (q, J = 7 Hz, 2 ethyl-CH_2), 4.82 (s, CH), 7.3 (m, 1 Ar-H), 7.45 (dd, J = 2 + 7.5 Hz, H at C-8), 7.7 (m, 1 Ar-H), 7.9 (dd, J = 2 + 7.5 Hz, H at C-5).

Anal. Calcd. for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.40; H, 5.05; N, 7.66.

Diethyl 2-(2-Oxo-3-nitro-1-phenyl-1,2-dihydroquinolin-4-yl)-malonate (**2b**).

This compound was prepared from **1b** (3.00 g, 10 mmoles) and diethyl malonate (3.20 g, 20 mmoles) using the procedure described for **2a**; the yield was 3.4 g (80%), colorless prisms, mp 103-104° (1-propanol); calorimetric data for thermolysis: onset 168.9°, peak 195.9°, ΔH -53 mcal/mg; ir: 1750 s, 1670 m cm^{-1}; ^{1}H nmr: δ 1.25 (t, J = 7.5 Hz, 2 ethyl-CH_3), 4.25 (q, J = 7.5 Hz, 2 ethyl-CH_2), 5.55 (s, CH), 6.7 (dd, J = 2 + 7 Hz, 1 Ar-H), 7.4-7.8 (m, 7 Ar-H), 7.9 (dd, J = 2 + 7 Hz, H at C-5).

Anal. Calcd. for $C_{22}H_{20}N_2O_7$: C, 62.26; H, 4.75; N, 6.60. Found: C, 62.44; H, 4.77; N, 6.54.

Diethyl 2-(2-Nitro-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*i,j*]quinolizin-1-yl)malonate (**2c**).

This compound was prepared from **1c** (2.65 g, 10 mmoles) and diethyl malonate (3.20 g, 20 mmoles) using the procedure described for **2a**, the yield was 3.77 g (97%), brown powder, mp 175-176° (ethanol); calorimetric data for thermolysis: onset 174.9°, peak 190.8°, ΔH -48 mcal/mg; ir: 1750 s, 1660 m cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.2 (t, J = 6 Hz, 2 ethyl-CH_3), 2.1-2.25 (m, CH_2), 3.0 (t, J = 6 Hz, 2 Ar-CH_2), 4.21-4.29 (m, 2 ethyl-CH_2 and NCH_2), 4.83 (s, CH), 7.15-7.25 (m, 1 Ar-H), 7.4 (dd, J = 2 + 7 Hz, H at C-8), 7.7 (dd, J = 2 + 7 Hz, H at C-10).

Anal. Calcd. for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.19; N, 7.21. Found: C, 58.77; H, 5.26; N, 7.05.

Dimethyl 2-(1-Methyl-3-nitro-2-oxo-1,2-dihydroquinolin-4-yl)-malonate (**3a**).

A mixture of **1a** (4.76 g, 20 mmoles), dimethyl malonate (5.28 g, 40 mmoles) and anhydrous potassium carbonate (6.0 g) in dimethylformamide (60 ml) was stirred at room temperature for 12 hours. The remaining solution was poured into ice/water (200 ml) and acidified with concentrated hydrochloric acid to *p*H = 1. After standing for about 5 hours the precipitate was filtered by suction and washed with water; the yield was 6.35 g (95%), yellow needles, mp 148-149° dec (toluene); calorimetric data for thermolysis: onset 182.8°, peak 187.2°, ΔH -87 mcal/mg; ir: 2850 m, 1740 s, 1660 m cm^{-1}; ^1H nmr: δ 3.7 (s, 2 OCH_3), 3.8 (s, NCH_3), 5.6 (s, CH), 7.45 (m, 1 Ar-H), 7.7-7.9 (m, 3 Ar-H).

Anal. Calcd. for $C_{15}H_{14}N_2O_7$: C, 53.90; H, 4.22; N, 8.38. Found: C, 54.11; H, 4.24; N, 8.16.

Dimethyl 2-(3-Nitro-2-oxo-1-phenyl-1,2-dihydroquinolin-4-yl)-malonate (**3b**).

This compound was prepared from **1b** (4.50 g, 15 mmoles), dimethyl malonate (3.96 g, 30 mmoles) and anhydrous potassium carbonate (4.5 g) using the procedure described for **3a**; the yield was 4.75 g (80%), yellow powder, mp 74-75° (methanol); calorimetric data for thermolysis: onset 172.4°, peak 188.8°, ΔH -65 mcal/mg; ir: 1750 s, 1670 s, 1600 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.8 (s, 2 ethyl-CH_3), 5.0 (s, CH), 6.75 (dd, J = 2 + 7 Hz, H at C-8), 7.2-7.7 (m, 7 Ar-H), 7.85 (dd, J = 2 + 7.5 Hz, H at C-5).

Anal. Calcd. for $C_{20}H_{16}N_2O_7$: C, 60.61; H, 4.07; N, 7.07. Found: C, 60.35; H, 3.98; N, 7.01.

Dimethyl 2-(2-Nitro-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*i,j*]quinolizin-4-yl)malonate (**3c**).

This compound was prepared from **1c** (5.30 g, 20 mmoles) and dimethyl malonate (3.96 g, 30 mmoles) using the procedure described for **3a**; the yield was 6.41 g (89%), yellow needles, mp 155° (ethanol); calorimetric data for thermolysis: onset 162.0°, peak 184.7°, ΔH -90 mcal/mg; ir: 1760 s, 1660 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.1-2.2 (m, CH_2), 3.0 (t, J = 6 Hz, Ar- CH_2), 3.8 (s, 2 OCH_3), 4.25 (t, J = 6 Hz, NCH_2), 4.88 (s, CH), 7.2-7.3 (m, 1 Ar-H), 7.4 (dd, J = 2 + 7 Hz, 1 Ar-H), 7.65 (dd, J = 2 + 7 Hz, 1 Ar-H).

Anal. Calcd. for $C_{17}H_{16}N_2O_7$: C, 56.67; H, 4.48; N, 7.77. Found: C, 56.72; H, 4.49; N, 7.70.

Ethyl 2-(1-Methyl-3-nitro-2-oxo-1,2-dihydroquinolin-4-yl)-acetate (**4a**).

A solution of **2a** (1.45 g, 4 mmoles) in 1,2-dichlorobenzene (30 ml) was heated under reflux for 1 hour. After cooling to room temperature the solvent was removed *in vacuo*. The residue was treated with hexane and the solid product filtered by suction; the yield was 0.48 g (42%), pale yellow needles, mp 211° (ethanol); ir: 1730 s, 1660 s, 1600 m cm^{-1}; ^1H nmr: δ 1.2 (t, J = 6.5 Hz, ethyl-CH_3), 3.77 (s, NCH_3), 4.1-4.2 (m, CH_2 and ethyl-CH_2), 7.5 (m, 1 Ar-H), 7.7 (dd, J = 2 + 7.5 Hz, H at C-8), 7.85 (m, 1 Ar-H), 8.05 (dd, J = 2 + 7.5 Hz, H at C-5).

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.94; H, 4.84; N, 9.77.

Ethyl 2-(3-Nitro-2-oxo-1-phenyl-1,2-dihydroquinolin-4-yl)-acetate (**4b**).

A solution of **2b** (0.59 g, 1.4 mmoles) in bromobenzene (20 ml) was heated under reflux for 5 hours. The solution was allowed to cool to room temperature, then the solvent was removed *in vacuo*. The residue was treated with diethyl ether/hexane and the precipitate filtered by suction; the yield was 0.29 g (60%), pale yellow prisms, mp 126-127° (ethanol); ir: 1740, 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, J = 6 Hz, ethyl-CH_3), 3.95 (s, CH_2), 4.25 (q, J = 7 Hz, ethyl-CH_2), 6.8 (dd, J = 2 + 7 Hz, H at C-8), 7.25-7.7 (m, 7 H, Ar-H), 7.8 (dd, J = 2 + 7 Hz, H at C-5).

Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 65.77; H, 4.58; N, 7.95. Found: C, 65.53; H, 4.65; N, 7.88.

1-Methoxycarbonyl-5-methylisoxazolo[3,4-*c*]quinoline-4(5*H*)-one (**5a**).

A solution of **3a** (1.50 g, 4.5 mmoles) was heated under reflux in 1,2-dichlorobenzene for 3 hours. Then the solvent was removed *in vacuo*, the residue treated with cyclohexane and the precipitate filtered by suction; yield 0.99 g (86%), colorless prisms, mp 210° (acetone); ir: 1730 s, 1670 m cm^{-1}; ^1H nmr: δ 3.65 (s, OCH_3), 4.1 (s, NCH_3), 7.4 (m, 1 Ar-H), 7.5-7.7 (m, 2 Ar-H), 8.95 (dd, J = 2 + 7 Hz, H at C-9); ^{13}C nmr: δ 152.9, 153.5 (C-3a, C-1), 154.8 (C-4), 157.2 (ester C=O).

Anal. Calcd. for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85. Found: C, 60.09; H, 3.94; N, 10.71.

11-Methoxycarbonyl-5,6-dihydro-4*H*-benzo[*i,j*]isoxaxolo[4,3-*b*]-quinolizin-8-one (**5c**).

A solution of **3c** (1.80 g, 5 mmoles) was heated under reflux in 1,2-dichlorobenzene (20 ml) for 3 hours. Then the solvent was removed *in vacuo*, the residue treated with cyclohexane and the precipitate filtered by suction; yield 1.00 g (70%), brown prisms, mp 232° (toluene); ir: 1730 s, 1670 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.0-2.15 (m, CH_2), 3.0 (t, J = 6 Hz, NCH_2), 4.1 (s, OCH_3), 4.27 (t, J = 6 Hz, Ar-CH_2), 7.1-7.4 (m, 2 Ar-H), 8.9 (dd, J = 2 + 7 Hz, H at C-7); ^{13}C nmr δ 152.6, 152.9 (C-8a, C-11), 154.8 (C-8), 157.3 (ester C=O).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.38; H, 4.18; N, 9.70.

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