CYCLIZATION OF PHENACYL 2-{[2,2-DI(ETHOXYCARBONYL)-VINYL]AMINO}BENZOATE

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Reaction of phenacyl anthranilate (**1**) with diethyl (ethoxymethylidene)malonate afforded phenacyl 2-{[2,2-di(ethoxycarbonyl)vinyl]amino}benzoate (**2**) which on heating in polyphosphoric acid underwent degradation. Thermal cyclization of **2** in diphenyl ether gave phenacyl 3-(ethoxycarbonyl)-4-oxo-1,4-dihydroquinoline-8-carboxylate (**4**). The phenacyl group did not cyclize even on prolonged heating at 250 °C. Heating in sulfuric acid resulted in hydrolysis of the ethyl ester under formation of 4-oxo-8-[(phenacyloxy)carbonyl]-1,4-dihydroquinoline-3-carboxylic acid (**6**). The structure of **4** was confirmed by an independent synthesis.

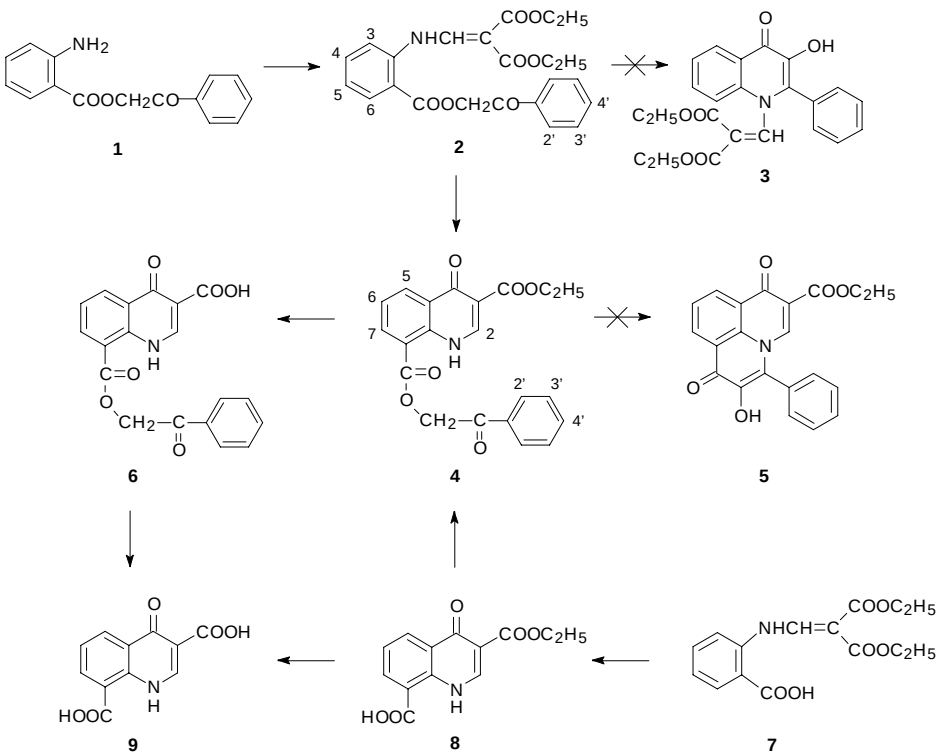
Key words: Thermal cyclization; Phenacyl aminobenzoate; Quinolones; Gould–Jacobs reaction.

Cyclization of (anilinomethylene)malonates giving rise to 4-oxo-1,4-dihydroquinoline-3-carboxylates[1,2], known as the Gould–Jacobs reaction, finds practical use in the synthesis of chemotherapeutics based on gyrase inhibitors[3]. Also known is the cyclization of phenacyl 2-aminobenzoates (phenacyl anthranilates) leading to 3-hydroxy-2-phenyl-4(1*H*)-quinolinones[4]. This reaction occurs with *N*-unsubstituted as well as *N*-monosubstituted phenacyl anthranilates[5]. Both reactions proceed thermally or on heating in polyphosphoric acid.

So far, there are no reports on reactions of compounds containing both these cyclizable groups. Therefore, we focused our attention on this alternative. The crucial question was which group cyclizes preferentially (under formation of compounds **3** or **4**) and whether the third ring subsequently closes giving rise to compound **5**. As a model compound for the cyclization we have chosen phenacyl 2-{[2,2-di(ethoxycarbonyl)-vinyl]amino}benzoate (**2**), obtained in high yield and purity by reaction of anthranilate **1** with diethyl (ethoxymethylidene)malonate (Scheme 1).

On attempted cyclization of substance **2** by heating in polyphosphoric acid, vigorous foaming and evolution of carbon dioxide took place at 90 °C. When the temperature of

120 °C was reached, the foaming ceased in 30 min. The reaction mixture contained several substances which were not identified. Further increase in temperature to 150 °C resulted in vigorous foaming and the reaction mixture continued to darken. In addition to a large quantity of a dark, ill-soluble resinous fraction, the mixture contained a small amount of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone (identified by TLC). The same result was obtained when the substance **2** was added to polyphosphoric acid preheated to 150 °C. The evolution of carbon dioxide suggests destruction of the malonate part of the molecule followed by other reactions. When compound **2** was subjected to thermal cyclization, only the (aminomethylidene)malonate part of the molecule cyclized under formation of quinolone **4** whereas the other part of the molecule did not cyclize even on prolonged heating. The structure of the compound was confirmed by ^{1}H NMR spectroscopy and by independent synthesis. The synthesis started from anthranilic acid which reacted with diethyl (ethoxymethylidene)malonate to give 2-{[2,2-di(ethoxycarbonyl)-vinyl]amino}benzoic acid (**7**). Acid **7** was thermally cyclized to quinolinedicarboxylic acid monoester **8**. The latter on reaction with phenacyl bromide was converted into compound **4** (Scheme 1).



SCHEME 1

Attempted further cyclization of phenacyl ester **4** to benzoquinolone **5** by heating in polyphosphoric acid failed, the major identified reaction product being acid **6**. This compound was also obtained by reaction of **4** with sulfuric acid (Scheme 1).

The above results suggest that the Gould–Jacobs cyclization is the major route and that the ring does not close even under relatively severe conditions. Although the cyclization of phenacyl anthranilate takes place at lower temperatures and the reaction proceeds more readily with *N*-unsubstituted compounds, it is affected by nitrogen substitution[5] as well as by the basicity of the amino group: the reaction proceeds more slowly or does not occur at all if the substituent at the nitrogen atom is bulky[5] and/or the basicity of the amino group is low[6]. The Gould–Jacobs reaction, on the other hand, is predominantly influenced by activation or deactivation of the aromatic ring[7]. In the system studied, the cyclization only leads to ethyl ester of substituted 4-hydroxy-3-quinolinecarboxylic acid. After heating of phenacyl esters **4** or **6** for several minutes in a sodium hydroxide solution, we identified the oxoquinolinedicarboxylic acid **9** in the reaction mixture. Product **9** was also obtained by hydrolysis of monoester **8**, which confirms the structure suggested for **4** and **6**.

The existence of tautomeric forms in derivative **4** was also investigated. The IR spectrum of its chloroform solution exhibits a band at 3 281 cm^{-1} due to the stretching vibration of N–H group hydrogen-bonded to the neighbouring carbonyl group. This hydrogen bonding is partly broken down in pyridine solution, as evidenced by appearance of bands at 3 286 cm^{-1} and at 3 413 cm^{-1}, the latter band being ascribed to the free N–H bond.

EXPERIMENTAL

Thin-layer chromatography was performed on Polygram Sil G/UV_{254} plates with UV detection at 254 nm. ^{1}H NMR spectra (δ, ppm; *J*, Hz) were measured on an AMX 360 instrument (Bruker) using 2% solutions in hexadeuteriodimethyl sulfoxide with TMS as internal standard. Melting points were determined on a Kofler block and are uncorrected. Infrared spectra (ν, cm^{-1}) of the compounds in KBr disks were scanned on an ATI Mattson Unicam FTIR spectrophotometer.

Phenacyl 2-{[2,2-Di(ethoxycarbonyl)vinyl]amino}benzoate (**2**)

A stirred suspension of anthranilate **1** (10.2 g, 42.3 mmol) in diethyl (ethoxymethylidene)malonate (10.8 g, 50 mmol) was gradually heated. The solid dissolved at 80 °C to a clear melt. After reaching 130 °C, the stirred mixture was kept at this temperature for 1.5 h. Toluene was added and the mixture was cooled to room temperature. After stirring for another 1 h, the deposited crystals were filtered, washed with cyclohexane and dried. Yield 16.3 g of crude benzoate **2** (including the product in the mother liquors). Crystallization from ethanol afforded 12.1 g (71%) of the product, m.p. 120–122 °C. For $C_{23}H_{23}NO_7$ (425.4) calculated: 64.93% C, 5.45% H, 3.29% N; found: 65.21% C, 5.43% H, 3.05% N. ^{1}H NMR spectrum: 1.22 t, 3 H, *J* = 7 (CH_3); 1.30 t, 3 H, *J* = 7 (CH_3); 4.9 2 × q, 4 H, *J* = 7 (2 × CH_2); 5.89 s, 2 H (CH_2CO); 7.35 dt, 1 H, *J* = 1.2 and 7 (H-5); 7.74–7.80 m, 5 H (H-3, H-4, 2 × H-3′, H-4′); 8.08 d, 2 H (2 × H-2′); 8.20 dd, 1 H, *J* = 1.2 and 7 (H-6); 8.58 d, 1 H, *J* = 13 (CH); 12.39 d, 1 H, *J* = 13 (NH). IR spectrum: 2 989, 2 933, 2 905 (CH), 1 703, 1 682 (CO), 1 648, 1 610 (C=C).

Phenacyl 3-(Ethoxycarbonyl)-4-oxo-1,4-dihydroquinoline-8-carboxylate (**4**)

Method A. Benzoate **2** (2 g, 4.7 mmol) was added to diphenyl ether (20 g) heated to 245 °C. After 45 min the starting substance was not detectable. The reaction mixture was then poured into cyclohexane (100 ml), cooled to room temperature, and the solid was collected (1.50 g). Crystallization from acetone and ethyl acetate afforded 1.02 g (57%) of quinolone **4**, m.p. 193–197 °C. For $C_{21}H_{17}NO_6$ (379.4) calculated: 66.49% C, 4.52% H, 3.69% N; found: 66.11% C, 4.64% H, 3.42% N. ^{1}H NMR spectrum: 1.32 t, 3 H, J = 7.1 (CH_3); 4.28 q, 2 H, J = 7.1 (CH_2); 5.94 s, 2 H (CH_2CO); 7.63–7.68 m, 3 H (2 × H-3′, H-4′); 7.78 t, 1 H, J = 7.1 (H-6); 8.10 d, 2 H, J = 7.1 (2 × H-2′); 8.56–8.59 m, 2 H (H-5, H-7); 8.71 s, 1 H (H-2); 12.1 bs, 1 H (NH).

Method B. A solution of phenacyl bromide (1.17 g, 5.92 mmol) in dimethylformamide (5 ml) was added dropwise to a mixture of compound **8** (1.66 g, 6.35 mmol), anhydrous potassium carbonate (1.0 g, 7.24 mmol) and dimethylformamide (30 ml) whereby the temperature of the mixture rose by 5 °C. After stirring for 2 h the mixture was poured into ice-cold water (200 ml). The formed precipitate was filtered off, washed with water and dried to give the product (0.82 g; 36%). The identity with the compound obtained by method *A* was confirmed by TLC and melting point measurement.

4-Oxo-8-[(phenacyloxy)carbonyl]-1,4-dihydroquinoline-3-carboxylic Acid (**6**)

Compound **4** (0.5 g, 1.32 mmol) was added to concentrated sulfuric acid (20 g). After heating at 105 °C for 20 min, no starting compound was detected by TLC. The reaction mixture was then poured into an ice–water mixture (150 g) and the separated white precipitate was collected and washed with water to neutral reaction of the washings. The crude substance was dried (0.46 g) and recrystallized to give 0.29 g (62%) of acid **6**, m.p. 252–254 °C. For $C_{19}H_{13}NO_6$ (351.3) calculated: 64.96% C, 3.73% H, 3.99% N; found: 64.67% C, 3.70% H, 3.82% N. ^{1}H NMR spectrum: 5.98 s, 2 H (CH_2); 7.65–7.78 m, 4 H (2 × H-3′, H-4′, H-6); 8.11 dd, 2 H, J = 1.3 and 7.9 (2 × H-2′); 8.58 d. 2 H, J = 7.9 (H-5, H-7); 8.71 s, 1 H (H-2).

2-{[2,2-Di(ethoxycarbonyl)vinyl]amino}benzoic Acid (**7**)

A mixture of anthranilic acid (6.85 g, 0.05 mol), diethyl (ethoxymethylidene)malonate (10.85 g, 0.05 mol) and ethanol (50 ml) was refluxed for 3.5 h. After this time no anthranilic acid could be detected by TLC. The solution was concentrated to about one half, the same volume of hexane was added, and the mixture was set aside at 5 °C. Isolation and drying afforded 11.8 g (77%) of acid **7**, m.p. 156–158.5 °C (reported[8] m.p. 156–157 °C). ^{1}H NMR spectrum: 1.30 2 × t, 6 H, J = 7.3 (2 × CH_3); 4.19 q, 2 H, J = 7.3 (CH_2); 4.28 q, 2 H, J = 7.3 (CH_2); 7.25 dt, 1 H, ^1J = 1.3, ^2J = 7.0 (H-5); 7.64–7.72 m, 2 H (H-3, H-4); 8.04 dd, 1 H, J = 7.0 and 1.3 (H-6); 8.55 d, 1 H, J = 13.6 (CH); 12.52 d, 1 H, J = 13.6 (NH). IR spectrum: 1 714, 1 680 (CO), 1 637, 1 608 (C=C).

3-(Ethoxycarbonyl)-4-oxo-1,4-dihydroquinoline-8-carboxylic Acid (**8**)

Acid **7** (2.0 g, 3.5 mmol) was added to simmering (250 °C) diphenyl ether (20 g), and the mixture was heated to the boil for 30 min. After this time the starting substance was no longer detected (TLC). The solution was poured into cyclohexane (100 ml) and cooled to room temperature. The separated precipitate was filtered off, washed with cyclohexane and dried to give 1.24 g of crude quinolone **8**. Recrystallization from acetic acid afforded 0.56 g (33%) of the product, m.p. 237–239 °C. For $C_{13}H_{11}NO_5$ (261.2) calculated: 59.76% C, 4.25% H, 5.36% N; found: 59.58% C, 4.30% H, 5.16% N. ^{1}H NMR spectrum: 1.32 t, 3 H, J = 7.1 (CH_3); 4.27 q, 2 H, J = 7.1 (CH_2); 7.56 t, 1 H, J = 8.0 (H-6); 8.41 dd, 1 H, J = 1.5 and 8.0 (H-5); 8.48 dd, 1 H, J = 1.5 and 8.0 (H-7); 8.76 d, 1 H, J = 7.0 (H-2); 12.38 d, 1 H, J = 7.0 (NH). IR spectrum: 3 271 (NH), 3 083 (ArH), 1 723 (CO), 1 616, 1 570 (C=C).

4-Oxo-1,4-dihydroquinoline-3,8-dicarboxylic Acid (**9**)

A solution of quinolone **8** (1.3 g, 5 mmol) in aqueous potassium hydroxide (2.8 g in 20 ml) was refluxed for 3 h. After cooling to room temperature, the mixture was acidified with dilute hydrochloric acid. The formed precipitate was collected, washed with distilled water and dried to give 0.98 g (84%) of dicarboxylic acid **9**; m.p. 340 °C (decomp.) (reported[9] m.p. 340–360 °C (decomp.)).

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