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Synthesis of 5- and 7-Nitro-3-hydroxyquinolin-2-ones

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A novel and efficient synthesis of 5- and 7-nitro-3-hydroxyquinolin-2-ones, from simple anilides, is presented, featuring the synthesis of the antibiotic agent viridicatin.

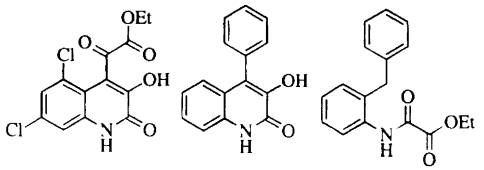
In connection with the development of an efficient procedure for the synthesis of 2,2′-biindolyl based on the double Madelung cyclisation of **1**, it was found that small amounts (5–10%) of 3-hydroxyquinolin-2-one (**2**) were formed.[1] This cyclisation was considered to be an intramolecular nucleophilic attack of the dianion **3** with *o*-toluidine as the leaving group (Fig. 1).

At this point it was argued that by introduction of more efficient leaving groups (e.g. methoxy) and/or by blocking the active hydrogen (NHCO) and/or by introduction of electron-withdrawing substituents or hetero atoms in the aromatic ring, the above reaction might be developed into a good synthesis of substituted 3-hydroxyquinolin-2-ones, and in this paper we report our results from such a study.

Results and discussion

Recently several synthetic 3-hydroxyquinolin-2-ones (e.g. **4**) have been demonstrated to have interesting biological activities as inhibitors of the glycine binding site associated with the NMDA-receptor.[2] These derivatives (Fig. 2) were prepared[3] via diazo intermediates. Another method that should merit further exploitation has been reported by Undheim.[4]

Viridicatin (**5**) is an alkaloid that has been isolated[5] from various species of *Penicillium* and synthesized previously by several routes,[6–8] including ring-expansion of isatin with phenyl diazomethane.[6] For the present approach, commercially available 2-benzylaniline was

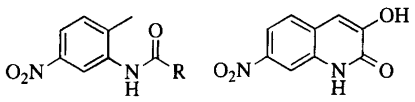


4 **5** **6**

Fig. 2. 3-Hydroxy-2-quinolones **4** and viridicatin **5** have interesting biological properties. The latter could be prepared from **6**.

acylated with ethyl oxalyl chloride yielding **6**, which in turn readily underwent cyclisation when treated with an excess of *t*-BuOK at 200 °C, giving viridicatin **5** in a good yield. Attempted cyclisations of **7a** did not proceed well, but the desired product **8** could be isolated in excellent yield (>90%) by a modified procedure involving treatment of **7b** with dimethyl oxalate and a suitable base at relatively low temperatures (25–50 °C) (Fig. 3).

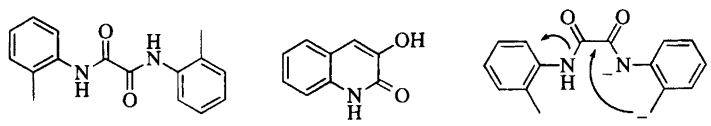
The reaction is believed to proceed as outlined in Scheme 1. Thus, the amide anion **9** is acylated to give



7a: R = COOEt
7b: R = H

8

Fig. 3. **7a** failed to cyclize to quinolone **8** but **7b** succeeded when treated with *tert*-BuOK–$(MeO_2C)_2$.



1 **2** **3**

Fig. 1. The quinolone **2**, was first prepared by Madelung starting from **1**.

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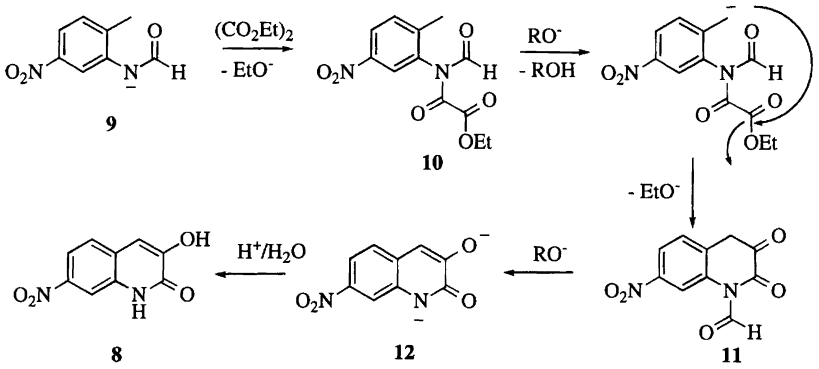


Scheme 1. Formation of 7-nitroquinolin-2-one from *N*-(2-methyl-5-nitrophenyl)formamide.

the imide **10** which in turn is deprotonated at the methyl carbon (activated by the nitro group). By way of an intramolecular attack at the ester carbonyl, ethoxide is expelled. Next, the *N*-formyl quinolone **11** formed, is deformylated by the ethoxide and upon treatment of the dianion **12** with water, the 3-hydroxy-7-nitroquinolin-2-one **8** is directly obtained as crystals.

3-Hydroxy-5-nitroquinolin-2-one (**13**) could be similarly prepared (Fig. 4). The pattern of substitution and the ready availability of this compound should render it an interesting candidate for syntheses of analogues belonging to the family of pyrrolo[4,3,2-*de*]quinoline alkaloids. Some of these alkaloids exhibit potent activities, including cytotoxicity and topoisomerase II inhibition. Discorhabdin C (**14**)[9] and damirone B (**15**)[10] are two examples.

The acetate **16** could also be obtained by heating the quinolone **8** in acetic anhydride (Fig. 5). Catalytic hydrogenation of 3-hydroxy-5-nitroquinolin-2-one (**13**) gave the expected amine **17a** but a few attempts to introduce a C_1-element between the 4-position and the amino nitrogen atom, e.g. cyclisation of the imidate **18** that could be prepared by heating **17a** in triethyl orthoformate, have so far not been successful.

It should be added that Wittman has previously synthesized[11] a derivative of **17a**, namely the 5-amino-3-ethoxy-6-methylquinolin-2-one (**17b**) by reacting 2,4-toluenediisocyanate with a suitable Wittig reagent, followed by alkaline hydrolysis of the intermediate product **19** (Fig. 5).

In connection with the development of the method according to Scheme 1, another approach towards quinolin-2-ones was also studied. It was argued that it should be possible to convert the stabilised mono-anion **20** of the corresponding imidate into the dianion **21** (Fig. 6), which might subsequently cyclize to 3,4-dihydro-2-ethoxy-7-nitroquinolin **22** in a fashion similar to the known[12] dimerization of this type of benzylic anion, which probably proceeds via radical intermediates (provide a radical scavenging dialkyl oxalate and the anion will cyclize intramolecularly to form an indole[12]).

In practice, a rather complex reaction mixture was obtained, but the oxidised product 2-ethoxy-7-nitroquinolin **23** could be readily isolated, although in a modest yield (as a fast mover) by column chromato-

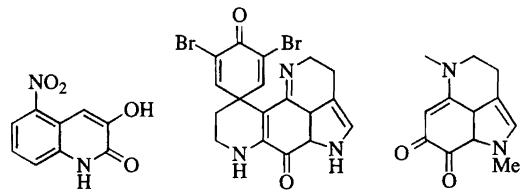


Fig. 4. Quinolone **13**, a candidate precursor towards marine alkaloids, e.g. discorhabdin C **14** and damirone B **15**.

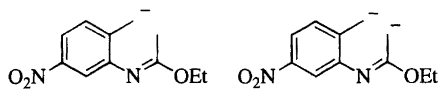
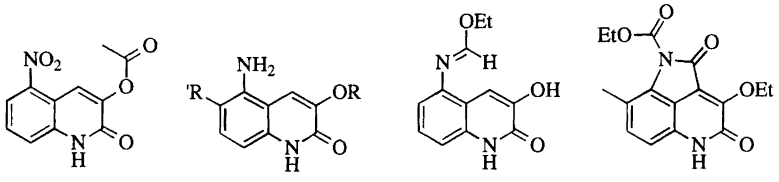


Fig. 6. Reactive anions of ethyl *N*-(2-methyl-5-nitrophenyl)-acetimidate.



17a: R = R' = H
17b: R = Et, R' = Me

Fig. 5. Various quinolin-2-ones.

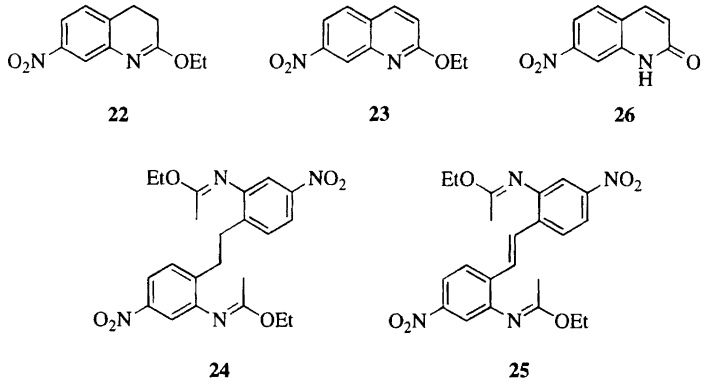


Fig. 7. Products from the reaction of ethyl *N*-(2-methyl-5-nitrophenyl)acetimidate with strong base.

graphy. Small amounts (< 5%) of the dimerisation products **24** and (the known[12]) **25** could be isolated as well (Fig. 7).

Acidic hydrolysis of **23** gave the known 7-nitroquinolin-2-one **26**, previously obtained by Sleiter via rearrangement of 7-nitroquinolin *N*-oxide.[13]

Experimental

Melting points were measured on a Reichert VME Kofler bench, IR-spectra were recorded with a Perkin Elmer 1600 FTIR, NMR-spectra with a Bruker AM400 or DPX300 spectrometer and mass spectra on a Micromass Platform II spectrometer with direct inlet at 70 eV.

Viridicatin (**5**). 2-Benzylaniline (9.15 g, 50 mmol) was dissolved in dioxane (35 ml), and methyl chlorooxalate (6.1 g, 50 mmol) was added dropwise to the solution which was stirred 2 h at 50 °C. The solution was then concentrated and poured into water, to provide *N*-(2-benzylphenyl)oxalamic acid methyl ester (**6**) as an oil that soon solidified. Yield 12.70 g (94%). The amide (5.38 g, 20 mmol) was mixed thoroughly with potassium *tert*-butoxide (5.70 g, 50 mmol) and heated (200 °C) for 15 min under a nitrogen atmosphere. After cooling, the reaction mixture was dissolved in water and acidified with acetic acid, giving a solid which was recrystallized from methanol to yield 3.85 g (82%). M.p. 267–268 °C (lit. m.p. 267–268 °C).[6]

*3-Hydroxy-5-nitro-1*H*-quinolin-2-one* (**13**). *N*-(2-Methyl-3-nitrophenyl)formamide (3.60 g, 20 mmol), dissolved in DMF (100 ml), was added dropwise to a cold (5 °C) mixture of potassium *tert*-butoxide (6.8 g, 60 mmol), dimethyl oxalate (7.0 g, 60 mmol) and DMF (50 ml). The resulting very dark blue–green coloured solution was warmed to 45 °C for 1 h and then poured into an ice–water mixture, slightly acidified with HCl. The quinolone 3.81 g (92%) could be collected as a pale yellow solid by filtration and washing with water. M.p. 301–303 °C. IR (KBr): 3080, 1687, 1527, 1341, 1288, 1238, 738, 647 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.44 (1 H, s), 10.43 (1 H, s), 7.86 (1 H, d), 7.59 (1 H, d), 7.57 (1 H, s), 7.44 (1 H, t). ^{13}C NMR (DMSO-d_6): δ 157.2 (s), 149.6 (s), 144.0 (s), 134.9 (s), 125.4 (d), 120.3 (d), 119.1 (d), 114.3 (s), 106.9 (d).

*3-Hydroxy-7-nitro-1*H*-quinolin-2-one* (**8**). (A) The same procedure as above was used, but with 2-methyl-*N*-(2-methyl-5-nitrophenyl)formamide (1.80 g, 10 mmol) as the substrate. Yield: 1.85 g (90%).

(B) Same as A, but with 2-methyl-*N*-(2-methyl-5-nitrophenyl)propionamide (2.10 g, 10 mmol) as the substrate. Yield 1.23 g (60%). M.p. 315–316 °C. IR (KBr): 3077, 1644, 1580, 1522, 1338, 1194, 898, 850, 732, 653, 621, 469 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.36 (1 H, s), 10.36 (1 H, s), 8.10 (1 H, s), 7.92 (1 H, d), 7.70 (1 H, s), 7.22 (1 H, d). ^{13}C NMR (DMSO-d_6): δ 158.2 (s), 149.4 (s), 144.6 (s), 132.8 (s), 126.6 (s), 126.5 (d), 116.4 (d), 111.3 (d), 109.8 (d).

*3-Acetoxy-5-nitro-1*H*-quinolin-2-one* (**16**). 3-Hydroxy-5-nitro-1*H*-quinolin-2-one (1.03 g, 5 mmol) was dissolved and heated in acetic anhydride (80 °C, 18 h). The product was collected by filtration and washed with acetic acid and water successively, which afforded 0.47 g (38%). M.p. 242–243 °C. IR (KBr): 1769, 1678, 1536, 1372, 1348, 1218, 1194, 1155, 902, 736, 668, 629 cm^{-1}. ^1H NMR (DMSO-d_6): δ 12.5 (1 H, s), 8.13 (1 H, s), 7.98 (1 H, d), 7.95 (1 H, s), 7.89 (1 H, d), 2.31 (3 H, s). ^{13}C NMR (DMSO-d_6): δ 167.9 (s), 156.6 (s), 147.3 (s), 143.2 (s), 136.6 (s), 129.1 (d), 127.2 (d), 123.2 (s), 116.3 (d), 110.2 (d), 21.1 (q). MS (*m/z*) (%): 248 (3), 206 (100), 176 (32), 160 (28), 132 (22), 104 (36), 77 (39), 51 (29), 43 (91).

*5-Amino-3-hydroxy-1*H*-quinolin-2-one* (**17a**). 3-Hydroxy-5-nitroquinolin-2-one (2.06 g, 10 mmol) was hydrogenated (50 psi) for 4 h in a Parr apparatus, using Raney nickel (1 g, 50%) as the catalyst and ethanol (200 ml) as the solvent. After completed reaction, acetic acid (50 ml) was added and the catalyst removed by filtration. The solvents were evaporated off leaving 1.3 g (74%) of the amine. M.p. 270–275 °C. IR (KBr): 3415, 3342, 2876, 1661, 1580, 1447, 1397, 1290, 1333, 883, 786, 723, 677 cm^{-1}. ^1H NMR (DMSO-d_6): δ 11.70 (1 H, s), 9.09

(1 H, s), 7.33 (1 H, s), 6.94 (1 H, t), 6.46 (1 H, d), 6.34 (1 H, d), 5.45 (2 H, s). ^{13}C NMR (DMSO-d_6): δ 158.7 (s), 144.0 (d), 134.0 (s), 126.9 (d), 108.5 (s), 107.4 (s), 106.2 (d), 102.8 (d).

N-*(2,3-Dihydroxyquinolin-5-yl)formimidic acid ethyl ester* (**18**). 5-Amino-3-hydroxy-1*H*-quinolin-2-one (0.18 g, 1 mmol) was heated (100 °C) with triethyl orthoformate (25 ml) for 2 weeks. The imidate was collected by filtration and washed with diisopropyl ether; 0.16 g (69%) was obtained. M.p. 246–248 °C. IR (KBr): 1636, 1574, 1235, 1184, 795, 658 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 11.95, (1 H, s), 9.45 (1 H, s), 7.95 (1 H, s), 7.23 (1 H, s), 7.18 (1 H, t), 7.03 (1 H, d), 6.68 (1 H, d), 4.33 (2 H, q), 1.34 (3 H, t). ^{13}C NMR (DMSO-d_6): δ 158.4 (s), 155.7 (d), 145.2 (s), 142.8 (s), 134.1 (s), 126.4 (d), 114.9 (s), 111.9 (d), 110.8 (d), 108.5 (d), 62.0 (t), 13.9 (q).

N-*(2-Methyl-5-nitrophenyl)acetimidic acid ethyl ester.* 2-Methyl-5-nitroaniline (7.60 g, 50 mmol) and triethyl orthoformate (20 ml) was heated at 120 °C for 48 h. The excess orthoester was removed with a rotary evaporator and the residue distilled under vacuum to yield a pale yellow oil that solidified upon standing, 4.54 g (41%). M.p. 43–44 °C. IR (KBr): 2979, 1670, 1517, 1348, 1288, 1243, 1052, 736 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.75 (1 H, dd, J=8.3 Hz, J'=2.3 Hz), 7.46 (1 H, d, J=2.3 Hz), 7.23 (1 H, d, J=8.3 Hz), 4.23 (2 H, q, J=7.1 Hz), 2.13 (3 H, s), 1.74 (3 H, s), 1.31 (3 H, t, J=7.1 Hz). ^{13}C NMR (DMSO-d_6): δ 161.6 (s), 148.7 (s), 146.8 (s), 137.1 (s), 130.6 (d), 117.7 (d), 115.2 (d), 61.9 (t), 18.1 (q), 16.4 (q), 14.1 (q). MS (*m/z*) (%): 222 (30), 177 (42), 163 (33), 152 (100), 117 (64), 106 (40), 89 (35), 77 (36).

2-Ethoxy-7-nitroquinoline (**23**). *N*-(2-Methyl-5-nitrophenyl)acetimidic acid ethyl ester (4.44 g, 20 mmol) was dissolved in DMA (35 ml) under a nitrogen atmosphere and potassium *tert*-butoxide (5.05 g, 45 mmol) was added in portions to the stirred mixture at 35 °C. After complete addition this temperature was kept for 1 h and finally the reaction mixture was heated to 70 °C for 2 h. After concentration of the solution, water and acetic acid (3 g, 50 mmol) were added and the resulting mixture extracted with diethyl ether. After evaporation of the extract the residue was chromatographed on silica gel, using methylene chloride as the eluent. The first fraction 1.75 g (40%) was collected. M.p. 130–131 °C. IR (KBr): 2290, 1611, 1530, 1459, 1350, 1304, 1272, 1036, 852, 760, 740 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 8.45–8.37 (2 H, m), 8.14–8.13 (2 H, m), 7.20 (1 H, d, J=8.9 Hz), 4.48 (2 H, q, J=7.0 Hz), 1.39 (3 H, t, J=7.0 Hz). ^{13}C NMR (DMSO-d_6): δ 163.1 (s), 147.9 (s), 145.1 (s), 139.2 (d), 129.7 (d), 128.6 (s), 121.9 (d), 117.5 (d), 116.8 (d), 62.0 (t), 14.3 (q). MS (*m/z*) (%): 218 (19), 203 (100), 190 (90), 174 (85), 116 (79), 89 (76).

Stilbene derivative (**25**). IR (KBr): 1669, 1510, 1336, 1293, 1255, 1050 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.85 (2 H, d), 7.75 (2 H, d), 7.50 (2 H, s), 7.24 (2 H, s), 4.26 (4 H, q), 1.78 (6 H, s), 1.33 (6 H, t). ^{13}C NMR (DMSO-d_6): δ 162.8 (s), 147.5 (s), 146.9 (s), 134.5 (s), 126.9 (d), 126.7 (d), 117.7 (d), 116.0 (d), 61.7 (t), 16.5 (q), 13.9 (q). MS [50 eV] (*m/z*) (%): 440 (1), 411 (8), 369 (7), 323 (9), 299 (19), 73 (18), 43 (100).

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