Synthesis of quinolonecarboxylic acids from 1,3,5-trinitrobenzene

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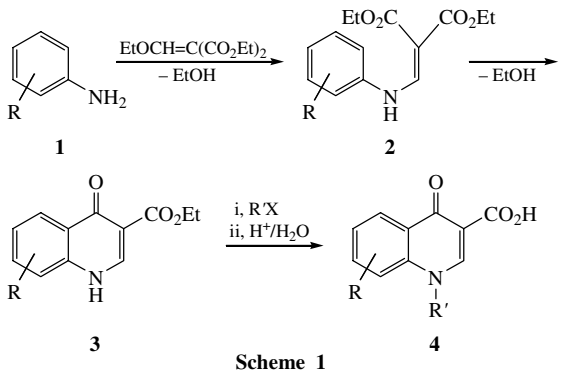
Products of nucleophilic substitution for one NO_2 group in 1,3,5-trinitrobenzene were selectively reduced to 3-X-5-nitroanilines (X = CF_3CH_2O, PhO, PhS), which were converted by condensation with $EtOCH=C(COOEt)_2$ to the respective enamines; acid-catalysed cyclization of the latter gives esters of X-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acids. The cyclization direction depends on the substituent type: *ortho* (X = CF_3CH_2O or PhO) or *para* (X = PhS) with respect to NO_2. N-Ethylation of these esters followed by hydrolysis gives the corresponding *N*-ethyl-5(7)-X-7(5)-nitroquinolinecarboxylic acids.

This study was carried out within the scope of 1,3,5-trinitrobenzene (TNB) utilisation as the key compound for synthesising polyfunctional benzannelated heterocycles, primarily heterocyclic systems among which valuable pharmaceuticals have been found. N-Substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acids (quinolonecarboxylic acids, QCA) are of particular interest in this respect. Compounds of this series show high antimicrobial activity, especially toward gram-negative bacteria. The mechanism of their action involves inhibition of DNA gyrase, a bacterial cell enzyme responsible for normal biosynthesis of bacterial DNA.[1]

Our goal was to synthesise QCA with a new combination of substituents from TNB.

One of the main methods for synthesising QCA is based on the Gould-Jackobs synthesis,[2] which involves condensation of substituted anilines **1** with ethoxymethylenemalonic ester to give enamine **2** followed by its thermal or acid-catalysed intramolecular cyclization (Scheme 1). Resulting QCA ester **3** is then hydrolysed to QCA. A substituent can be introduced to the nitrogen atom at any stage, but it is often more convenient to introduce an N-substituent to the molecule of ester **3** followed by hydrolysis to N-substituted QCA (Scheme 1).



Scheme 1

The cyclization direction is sensitive to both electronic and spatial factors.[2]

In order to synthesise nitroquinolonecarboxylic acids with different substituents in the benzene fragment based on TNB, we first replaced a nitro group in TNB by treatment with three different anionic nucleophiles (Scheme 2) using known techniques.[3–5]

One of the nitro groups in resulting 1-X-3,5-dinitrobenzenes **5** was selectively reduced to give 3-X-5-nitroanilines **6**,† which gave enamines **7** on heating with an equimolar amount of ethoxymethylenemalonic ester.‡ Compounds **7** were used for intramolecular cyclization: their treatment with a mixture of $POCl_3$ and polyphosphoric acid gave ethyl esters of X-substituted nitroquinolonecarboxylic acids in 40–55% yields. Note that intramolecular cyclization can principally occur at both *ortho* and *para* positions with respect to the NO_2 group (*para* and *ortho* positions with respect to the X group, respectively) to give corresponding esters **8′** or **8″** or their mixtures (Scheme 2).§

We have found that only one isomer is formed in each case (the ^{1}H NMR data are reported for the crude reaction product). The mutual arrangement of substituents in esters **8** was proven by studying products of further conversion. Since, as noted above, N-substituted QCA[6,7] are the most interesting in terms of anti-

† The compounds were characterised by ^{1}H NMR spectra, electron-impact mass spectra, and satisfactory elemental analyses. ^{1}H NMR spectra were recorded on Bruker AC-250 and RX-500 spectrometers in [$^2H_6$]DMSO solutions. Mass spectra were obtained using a Kratos MS-30 instrument. The spectra of all the compounds contained a molecular ion peak (M^+). The course of the reactions was monitored by TLC on Silufol UV-254.

General procedure for the synthesis of 1-X-3-amino-5-nitrobenzenes **6**. Hydrazine hydrate (10 ml, 0.2 mol) was added to a mixture of an appropriate 1-X-3,5-dinitro compound (0.1 mol), $FeCl_3 \cdot 6H_2O$ (0.19 g, 0.5 mmol) and activated carbon (2.6 g) in methanol (250 ml). The reaction mixture was refluxed until the parent dinitro compound was converted (TLC monitoring with $CHCl_3$ as the eluent). The reaction mixture was filtered while hot and the carbon was washed with hot methanol (2×50 ml) on the filter; the filtrate was cooled to +4 °C. The resulting precipitate was filtered off. The resulting compounds are listed below.

6a: reaction time, 7 h; yield 86%; mp 104–105 °C. ^{1}H NMR, δ: 4.76 (q, 2H, ^3J 9 Hz), 5.86 (s, 2H), 6.61 (s, 1H), 7.01 (s, 1H), 7.12 (s, 1H).

6b: reaction time, 3 h; yield 65%; mp 120–121.5 °C. ^{1}H NMR, δ: 5.95 (s, 2H), 6.57 (s, 1H), 6.82 (s, 1H), 7.12 (s, 1H), 7.14 (m, 4H), 7.44 (t, 2H, ^3J 8 Hz).

6c: reaction time, 2.5 h; yield 73%; mp 102–104 °C. ^{1}H NMR, δ: 5.98 (s, 2H), 6.67 (s, 1H), 7.07 (s, 1H), 7.28 (s, 1H), 7.41 (m, 5H).

‡ *General procedure for the synthesis of compounds* **7**. A mixture of an appropriate 1-X-3-amino-5-nitrobenzene (0.01 mol) and ethoxymethylenemalonate (2.16 g, 0.01 mol) was heated to 120 °C and kept until the parent aminonitro compound was converted (TLC monitoring with $CHCl_3$ as the eluent). The reaction mixture was cooled to room temperature and dried *in vacuo*. The resulting compounds are listed below.

7a: reaction time, 2 h; yield 100%; oil. ^{1}H NMR, δ: 1.23 (m, 6H), 4.2 (m, 4H), 4.95 (q, 2H, ^3J 8 Hz), 7.58 (s, 1H), 7.62 (s, 1H), 7.95 (s, 1H), 8.42 (d, 1H, ^3J 14 Hz), 10.15 (d, 1H, ^3J 14 Hz).

7b: reaction time, 3 h; yield 100%: oil. ^{1}H NMR, δ: 1.26 (m, 6H), 4.17 (m, 4H), 7.16 (d, 2H, ^3J 8 Hz), 7.27 (t, 1H, ^3J 8 Hz), 7.36 (s, 1H), 7.5 (m, 3H), 7.99 (s, 1H), 8.31 (d, 1H, ^3J 14 Hz), 10.64 (d, 1H, ^3J 14 Hz).

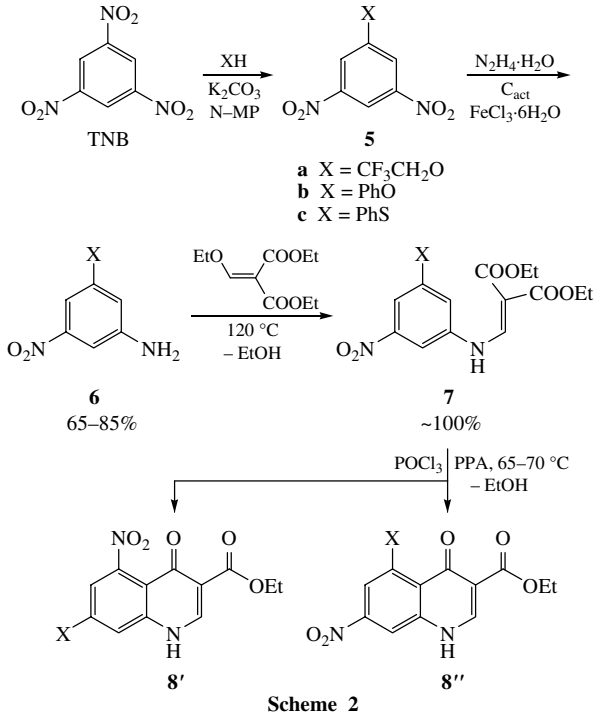
7c: reaction time, 2 h; yield 100%; oil. ^{1}H NMR, δ: 1.25 (m, 6H), 4.18 (m, 4H), 7.5 (m, 6H), 7.68 (s, 1H), 8.08 (s, 1H), 9.08 (d, 1H, ^3J 14 Hz), 10.12 (d, 1H, ^3J 14 Hz).

§ *General procedure for the synthesis of esters* **8**. Polyphosphoric acid (24 g) was added with continuous stirring to a solution of an appropriate enamine **7** in $POCl_3$ (35 ml). The reaction mixture was heated to 65–70 °C and kept with continuous stirring until the parent compound was converted (TLC monitoring with $CHCl_3$ as the eluent). The reaction mixture was poured onto 300 ml of ice. The precipitate formed was filtered off and crystallised from a minimum of DMF (from γ-butyrolactone in the case of compound **8″c**). The resulting compounds are listed below.

8′a: reaction time, 6 h; yield 57%; mp 272–275 °C. ^{1}H NMR, δ: 1.28 (t, 3H, ^3J 8 Hz), 4.21 (q, 2H, ^3J 8 Hz), 5.01 (q, 2H, ^3J 9 Hz), 7.32 (s, 1H), 7.53 (s, 1H), 8.55 (s, 1H), 12.32 (s, 1H).

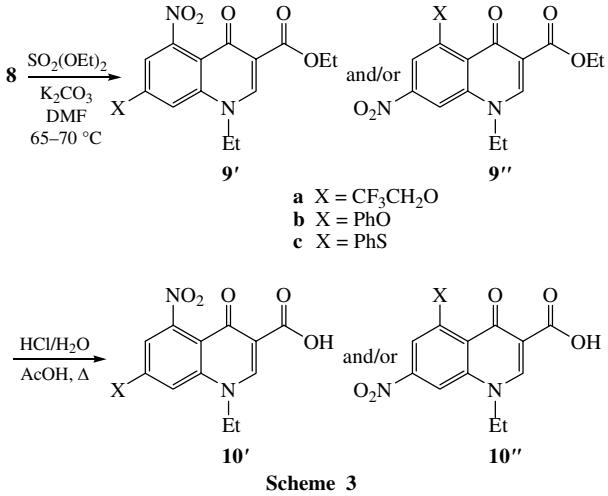
8′b: reaction time, 7.5 h; yield 39%; mp 284–285 °C. ^{1}H NMR, δ: 1.25 (t, 3H, ^3J 8 Hz), 4.21 (q, 2H, ^3J 8 Hz), 7.12 (s, 1H), 7.32 (m, 3H), 7.52 (m, 2H), 8.52 (s, 1H), 12.38 (s, 1H).

8″c: reaction time, 8 h; yield 53%; mp 290–291 °C. ^{1}H NMR, δ: 1.3 (t, 3H, ^3J 8 Hz), 4.24 (q, 2H, ^3J 8 Hz), 7.1 (s, 1H), 7.62 (s, 5H), 8.09 (s, 1H), 8.62 (s, 1H), 12.55 (s, 1H).



Scheme 2

bacterial activity, we conducted N-ethylation of QCA esters **8** obtained with diethyl sulfate in the presence of K_2CO_3 in DMF (Scheme 3).



Scheme 3

Resulting *N*-ethyl derivatives **9** were treated by acidic hydrolysis without purification to give target nitroquinolonecarboxylic acids **10** (yields ~65–80%).¶ The mutual arrangement of the substituents in nitroquinolonecarboxylic acids **10** was determined in an ^{1}H NMR NOE experiment. For compound **10a**: coupling is observed between the protons of the methylene fragment of the trifluoroethyl moiety and protons at the 6- and 8-positions of the nitrobenzene ring, and hence the CF_3CH_2O group is located at the 7-position and the NO_2 group is at C-5, structure **10′a** (only interaction with H-6 would have been observed for the alternative arrangement). In the case of **10b**, coupling between protons of the PhO substituent and the protons H-6 and H-8 of the nitrobenzene moiety, as well as the protons of the CH_2 fragment of the *N*-ethyl group, is observed. Hence, the PhO is located at the 7-position and the NO_2 group is at C-5, structure **10′b**. In the case of **10c**, protons of the PhS substituent are coupled only with the H-6 protons of the nitrobenzene fragment and the protons of the CH_2 fragment in the *N*-ethyl substituent are coupled with the H-2 and H-8 protons; hence, the PhS substituent is located at the 5-position and the NO_2 group is at C-7, structure **10″c**.

Thus, the cyclization of enamines **7** (Scheme 2) occurs at the *ortho* position to NO_2 in the case of $X = CF_3CH_2O$ or PhO (structure **8′**) or at the *para* position to NO_2 in the case of X = PhS (structure **8″**). In other words, the cyclization of enamines **7** occurs selectively but its direction depends on the type of substituent X.

It should be noted that synthesis of QCA with nitro groups at the 5- and 7-positions by intramolecular cyclization has not been reported before.

The antimicrobial activity of QCA **10** was studied *in vitro* at the Russian State Scientific Centre for Antibiotics. The details will be published later, but it may be said preliminarily that at least in one case (X = PhO), activity for gram-positive bacteria is observed, which is unusual for the known QCAs. This result may be useful for creating drugs of the QCA series efficient toward gram-positive bacteria.

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¶ *General procedure for the synthesis of QCA* **10**. K_2CO_3 (5.52 g, 0.04 mol) was added with continuous stirring to a solution of compound **8** (0.01 mol) in DMF (40 ml). The reaction mixture was heated to 65–70 °C and kept for 30 min at this temperature; $SO_2(OEt)_2$ (1.54 g, 0.01 mol) was then added. The mixture was cooled to room temperature and kept until the parent compound was converted (TLC monitoring; eluent, $CHCl_3$). The solvent was distilled off *in vacuo* and the solid residue was extracted with ethyl acetate. The extract was washed with water (3×100 ml) and evaporated to dryness. The solid residue was placed in a mixture of concentrated hydrochloric acid (36%, 15 ml) and AcOH (15 ml) and refluxed for 2 h. The resulting precipitate was filtered off and dried in the air. The resulting compounds are listed below.

10′a: reaction time, 4 h; yield 76%; mp 266–268 °C. ^{1}H NMR, δ: 1.45 (t, 3H, ^3J 8 Hz), 4.61 (q, 2H, ^3J 8 Hz), 5.12 (q, 2H, ^3J 9 Hz), 7.68 (s, 1H), 7.89 (s, 1H), 9.08 (s, 1H), 14.15 (s, 1H).

10′b: reaction time, 6 h; yield 64%; mp 327–329 °C. ^{1}H NMR, δ: 1.32 (t, 3H, ^3J 8 Hz), 4.5 (q, 2H, ^3J 8 Hz), 7.31 (m, 3H), 7.52 (t, 2H, ^3J 8 Hz), 7.65 (s, 1H), 7.72 (s, 1H), 9.09 (s, 1H), 14.1 (s, 1H).

10″c: reaction time, 3 h; yield 78%; mp 273–275 °C. ^{1}H NMR, δ: 1.42 (t, 3H, ^3J 8 Hz), 4.65 (q, 2H, ^3J 8 Hz), 7.29 (s, 1H), 7.65 (s, 5H), 8.28 (s, 1H), 9.12 (s, 1H), 14.21 (s, 1H).