# NOVEL SYNTHESIS OF 3-NITRO-4-QUINOLONE DERIVATIVES

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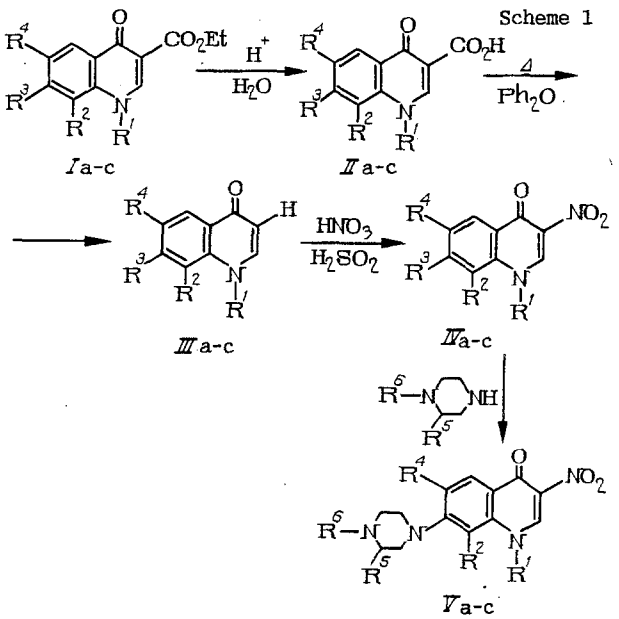
The problem of the selective introduction of the nitro group into π-electron-deficient nitrogen heterocycles has not been clearly resolved to date. This circumstance makes the task of developing preparative methods for the synthesis of 3-nitro-4-quinolones a vital one, as it has been previously. 3-Nitroquinoline derivatives are of interest for pharmacological research as potential drugs and also as convenient key products for the preparation of biologically active compounds.

We previously developed an original method for the synthesis of 3-nitro-4-quinolone derivatives from α-nitroacetophenones [4]. In addition, the Niementowski synthesis of 3-nitroquinolones [5] is known and widely used. Each of these methods has its particular limitations. Moreover, a large number of quinolone-3-carboxylic acids have been reported up to the present time, and an active investigation on antibacterial compounds is being conducted amongst the derivatives of these acids [7]. We have investigated the possibility of preparing 3-nitro-4-quinolones from 4-quinolone-3-carboxylic acids, and a suitable method of synthesis has been developed (Scheme 1).

Scheme 1



$R^1$=Et (Ia–Va, Ic–Vc), cyclopropyl (Ib–Vb);
$R^2$=H (Ia–Va, Ib–Vb), F (Ic–Vc);
$R^3$=Cl (Ia–Va, Ib–Vb), F (Ic–Vc);
$R^4$=$NO_2$ (Ia–Va, Ib–Vb), F (Ic–Vc);
$R^5$=H (Va, b), Me (Vc); $R^6$=Me (Va, b), H (Vc).

The initial compounds – ethyl quinolone-3-carboxylates (I) – undergo acid hydrolysis and subsequent decarboxylation by heating at 250°C in diphenyl oxide. It should be noted that attempts to carry out the decarboxylation of acids (II) by heating in DMF, quinoline, or with these reagents in the presence of both cupric oxide and metallic copper were not successful. The decarboxylation of acids II occurs quite slowly, and in order to isolate 4-quinolones III in a pure state a further stage for the removal of initial acids II from the

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TABLE 1. Physicochemical and Spectroscopic Parameters of Compounds III-V

| Compound | Empirical formula | Temperature, °C | Yield, % | $^1$H chemical shift, ppm | | | | | | SSCC, Hz |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | H-2 | H-3 | H-5 | H-8 | R$^1$ | other groups | |
| IIIa | $C_{11}H_9ClN_2O_3$ | 237—40 | 79,2 | 8,12 | 6,21 | 8,72 | 8,16 | $CH_2$:4,34<br>$CH_3$:1,34 | — | $^3J(H_2H_3)=7,9$ |
| IIIb | $C_{12}H_8ClN_2O_3$ | 203—5 | 87,7 | 8,04 | 6,08 | 8,65 | 8,21 | CH:3,56<br>$CH_2$:1,1—1,3 | — | $^3J(H_2H_3)=8,0$ |
| IIIc | $C_{11}H_8F_3NO$ | 113—5 | 61,4 | 8,03 | 6,12 | 7,93 | — | $CH_2$:4,33<br>$CH_3$:1,38 | — | $^3J(FH_5)=10,7$ $J(FCH_2)=3,5$<br>$^4J(FH_5)=8,6$ $J(FCH_3)=1,4$ |
| IVa | $C_{11}H_8ClN_3O_5$ | 270—5 | 93,4 | 9,48 | — | 8,85 | 8,39 | $CH_2$:4,56<br>$CH_3$:1,41 | — | $^5J(FH_5)=2,3$ $^3J(H_2H_3)=7,8$ |
| IVb | $C_{12}H_8ClN_3O_5$ | 196—8 | 90,0 | 9,13 | — | 8,84 | 8,47 | CH:3,83<br>$CH_2$:1,1—1,3 | — | |
| IVc | $C_{11}H_7F_3N_2O_3$ | 182—90 | 73,5 | 9,39 | — | 8,14 | — | $CH_2$:4,55<br>$CH_3$:1,46 | — | $^3J(FH_5)=10,5$ $J(FCH_2)=3,6$<br>$^4J(FH_5)=8,4$ $J(FCH_3)=1,5$ |
| Va | $C_{16}H_{19}N_5O_5$ | 248—50 | 72,0 | 9,34 | — | 8,57 | 7,17 | $CH_2$:4,49<br>$CH_3$:1,40 | $CH_3$:2,22<br>$R^3$:2,45<br>3,19 | $^5J(FH_5)=2,2$ |
| Vb | $C_{17}H_{19}N_5O_5$ | 241—2 | 62,5 | 9,02 | — | 8,58 | 7,58 | CH:3,80<br>$CH_2$:1,2—1,4 | $CH_3$:2,25<br>$R^3$:2,44<br>3,20 | |
| Vc | $C_{16}H_{17}F_2N_3O_3$ | 175—3 | Quant. | 9,27 | — | 7,81 | — | $CH_2$:4,51<br>$CH_3$:1,44 | $CH_3$:1,01<br>$R^3$:2,8—3,4 | $^3J(FH_5)=12,3$ $J(FCH_2)=3,8$<br>$^5J(FH_5)=1,8$ $J(FCH_3)=1,3$ |

reaction products is necessary. The quinolones III, which are unsubstituted at the 3-position, undergo nitration under relatively mild conditions to form 3-nitro-4-quinolones IV. The reaction is carried out in concentrated sulfuric acid, with fuming nitric acid being added to the solution at 0°C. It it interesting to note that nitration occurs smoothly even for quinolones that have powerful deactivators of electrophilic substitution – a nitro group or 3 fluorine atoms – in the benzene ring. Moreover, the presence of these substitutents makes it possible to carry out nitration more selectively, with the result that we have isolated the 3-nitro derivatives IV as the sole reaction products.

It should be emphasized that introduction of nitro groups into the 3- and 6-positions assists the facile nucleophilic substitution of halogen atoms at the 7-position of the quinoline ring to give compounds Va-c. On addition of N-methylpiperazine in acetonitrile to a solution of 7-chloro-3,6-dinitroquinolone (IVa), exothermic substitution of the chlorine atom is accompanied by tar formation. The reagents are therefore mixed while cooled and the reaction mixture is then brought to the boil. Under these conditions the reaction occurs more specifically and in high yield.

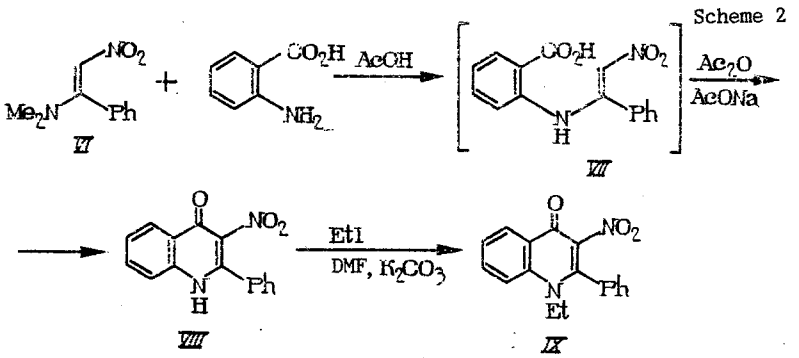
The structures of all the synthesized compounds were confirmed by $^1$H NMR. The spectroscopic parameters for compounds III-V are given in Table 1. Assignment of most of the signals in the spectrum of these compounds is clearly made on the basis of their chemical shifts, spin–spin coupling constants (SSCC), and multiplicity. An exception to this is assignment of the signals due to H(2) and H(5), which have similar chemical shifts for a number of compounds.

In order to assign these signals, the nuclear Overhauser effects (NOE) from the methylene protons of the ethyl group at the 1-position were recorded. Positive NOE values indicate the spatial proximity (< 3 Å) of the interacting nuclei. The high NOE values for H(2) and H(8) made it possible for a definite assignment of these signals to be made (see Table 1). It should be noted that spin–spin coupling occurs between the protons of the ethyl group and the fluorine nucleus at the 8-position of the quinoline ring in the $^1$H NMR spectra of the fluoro derivatives Ic-Vc.

The high values of these SSCC (see Table 1) and the considerable distance between the chemical bonds of the interacting nuclei suggest an unusual spin–spin coupling through space [2], which occurs because of the spatial proximity of the ethyl group to the fluorine atom.

An alternative approach to the synthesis of 3-nitro-4-quinolones was achieved by us in the the case of 1-alkyl-2-phenyl-3-nitro-4-quinolones (IX) (Scheme 2). The Niementowski method

Scheme 2




for the synthesis of 3-nitro-4-quinolones (from anthranilic acids and dipotassium metazonate) [5] is familiar, as is its modification, which uses 2-dimethylamino-3-nitropropene as the nitro synthon. This method was used in a similar manner to 2-methyl-3-nitro-4-quinolone derivatives for synthesis of the 3-nitroquinolone VIII, containing a phenyl substituent at the 2-position, from the nitroenamine VI, which we had previously obtained [1], and anthranilic acid. Transamination of the initial enamine VI in acetic acid is sufficiently complete according to the results of TLC. A mass spectrometric study of the resulting product also suggests that the intermediate nitroenamine VII is formed, but it was not possible to isolate it in a pure state. In addition, treatment of the resulting compound VII with acetic anhydride in the presence of sodium acetate gives the required nitroquinolone VIII.

Ethylation of 2-phenyl-3-nitro-4-quinolone (VIII) is carried out with ethyl iodide in DMF in the presence of potassium carbonate. With the conditions which we have selected it is usually possible to obtain N-substituted derivatives [3, 6]. The spectroscopic data (UV, NMR, and mass spectra) suggest that in this case alkylation occurs on the nitrogen atom with the formation of 1-ethyl-2-phenyl-3-nitro-4-quinolone (IX). In a study of the antibacterial activity of IV-V and VIII-IX, none of the compounds were found to be of practical interest.

## EXPERIMENTAL

The NMR spectra were recorded on an XL-200 spectrometer (Varian, USA) with working frequency of 200.05 Hz for $^1H$ nuclei. The internal standard for recording the $^1H$ chemical shifts was TMS. The spectra of the compounds under study were recorded in DMSO-$d_6$ solution. The UV spectra (in ethanol) were recorded on a Perkin–Elmer 575 spectrophotometer. The elemental analysis data corresponded to the calculated values. The physicochemical properties of compounds III-V are listed in Table 1.

1-Ethyl-6-nitro-7-chloro-4-quinolone-3-carboxylic Acid (IIa). To 5 g (0.0154 mole) of ethyl 1-ethyl-6-nitro-7-chloro-4-quinolone-3-carboxylate (Ia) was added 45 ml of a three-component mixture of concentrated HCl, AcOH, and water (1:1:1). The reaction mixture was boiled for 3 h and cooled, and the precipitate that had formed was filtered off and washed with $CH_2Cl_2$. Yield was 4.5 g (98.5%) of compound IIa. Compounds IIb and IIc were obtained in a similar manner.

1-Ethyl-4-oxo-6-nitro-7-chloro-1,4-dihydroquinoline (IIIa). To 4 g (0.0135 mole) of IIa was added 40 ml of diphenyl oxide, and the mixture was refluxed for 10 h at 250-255°C, coole , and supplemented with 50 ml of petroleum ether. The precipitate that formed was filtered off, washed with a small quantity of petroleum ether, and dried. The precipitate of IIIa was then dissolved in 100 ml of $CHCl_3$, washed with an aqueous solution of potassium carbonate (20 ml), and the chloroform extract was dried over $Na_2SO_4$. The solvent was then evaporated off, the residue was ground with ether, and the precipitate was filtered off. Yield was 2.7 g (79.2%) of compound IIIa. Compound IIIb was obtained in a similar manner.

1-Ethyl-4-oxo-6,7,8-trifluoro-1,4-dihydroquinoline (IIIc). To 3.5 g (0.0129 mole) of IIc was added 35 ml of diphenyl oxide, and the mixture was refluxed for 10 h at 250-255°C, cooled, and supplemented with 45 ml of petroleum ether. The precipitate that formed was filtered off, washed with a small quantity of petroleum ether, and dried. To the precipitate was then added 100 ml of water, the mixture was boiled for 15 min, the hot suspension was filtered, and the precipitate was dried. Yield was 1.8 g (61.4%) of compound IIIc.

1-Ethyl-3,6-dinitro-4-oxo-7-chloro-1,4-dihydroquinoline (IVa). To 5 g (0.02 mole) of compound IIIa in 50 ml of concentrated sulfuric acid on cooling with ice was added dropwise 15 ml of fuming $HNO_3$. The mixture was maintained for 30 min, the cooling was then stopped, and the reaction mixture was left at room temperature for 2 h, poured on to ice, and the precipitate that formed was filtered off. Yield was 5.5 g (93.4%) of compound IVa. Compounds IVb and IVc were obtained in a similar manner.

1-Ethyl-3,6-dinitro-4-oxo-7-(4-methylpiperazino)-1-dihydroquinoline (Va). To 0.5 g (0.0017 mole) of IVa in 5 ml of acetonitrile at room temperature was added 1 ml (0.085 mole) of N-methylpiperazine, the mixture was agitated at 60°C for 1 h and cooled to 0-2°C, and the precipitate that formed was filtered off. Yield was 0.44 g (72%) of compound Va. Compound Vb was obtained in a similar manner.

1-Ethyl-3,6-dinitro-4-oxo-7-(3-methylpiperazino)-1,4-dihydroquinoline (Vc). To 0.7 g (0.0026 mole) of IVc in 5 ml of acetonitrile was added 0.4 g (0.004 mole) of 2-methylpiperazine with agitation, the mixture was refluxed for 1 h and cooled, the solvent was evaporated off, the oily residue was ground with ether, and the precipitate was filtered off. Yield was 0.9 g of compound Vc.

2-Phenyl-3-nitro-4-oxo-1,4-dihydroquinoline (VIII). A mixture of 15 g (0.0781 mole) of nitroenamine VI and 11.7 g (0.0854 mole) of anthranilic acid in 150 ml of glacial AcOH was heated at 90°C for 1 h with agitation; the reaction mixture was then cooled and the AcOH was evaporated off. The oily precipitate of compound VII was dissolved in 76 ml of $Ac_2O$ and was heated with vigorous agitation to 110°C and 8.2 g (0.100 mole) of molten AcONa was then added. The mixture was refluxed for 1 h at 138-140°C and cooled, and the precipitate that formed was filtered off, washed with 50 ml of AcOH followed by 50 ml of water,

and dried. Yield was 4 g (20%) of compound VIII. UV spectrum (in ethanol), $\lambda_{max}$ (log $\varepsilon$): 214.5 (4.41), 241 (4.46), 319 (4.03), 333 (4.03) nm. $^1$H NMR spectrum (DMSO-$d_6$): 5-H 8.24 d; 6-H 7.51 t; 7-H 7.82 t; 8-H 7.7 d; Ph 7.64.

1-Ethyl-2-phenyl-3-nitro-4-oxo-1,4-dihydroquinoline (IX). A mixture of 1 g (0.0038 mole) of 2-phenyl-3-nitro-4-quinoline (VIII), 0.8 g (0.0058 mole) of calcined potash, and 18 ml of DMF was heated with agitation to 80°C, 1.16 g (0.0074 mole) of EtI was then added, the mixture was heated to 100°C for 3 h, 1.16 g (0.0074 mole) of EtI was added, and the mixture was heated at 100°C for a further hour and left overnight at room temperature. The DMF was distilled off under vacuum, the residue was diluted with 50 ml of water and extracted with $CH_2Cl_2$ (2 × 50 ml), the combined extracts were dried over $Na_2SO_4$, the solvent was evaporated, the oily residue was ground with isopropanol, and the precipitate was filtered off. Yield was 0.4 g (45%) of compound IX. UV spectrum (in ethanol), $\lambda_{max}$ (log $\varepsilon$): 214 (4.47), 232 (4.48), 320 (4.13), 330 (4.13) nm. $^1$H NMR spectrum (DMSO-$d_6$): 5-H 8.38 d; 6-H 7.63 t; 7-H 8.02 t; 8-H 8.01; Ph 7.62; Et: $CH_2$ 4.08, $CH_3$ 1.21.

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# SYNTHESIS OF 3-ACYL-5-HYDROXYINDOLES AND 3-ACYL-5-HYDROXYBENZOFURANS. INFLUENCE OF SOLVENT ON THE COURSE OF THE NENITZESCU REACTION


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The Nenitzescu reaction, which is the interaction of quinones with enamines, is the most general method for the synthesis of 5-hydroxyindoles. In a number of cases, 5-hydroxybenzofurans are also formed, and depending upon the selected objectives and conditions of the process, one or the other direction of the reaction prevails [14].

The Nenitzescu reaction possesses unquestionable interest for the synthesis of compounds possessing high biological activity [1, 10]. In connection with this, an understanding of the mechanism of the reaction taking place upon interaction of quinones with different enamines, and an exploration of the possibility of the directed synthesis of both 5-hydrobenzofuran and 5-hydroxyindole derivatives in the synthetic and theoretical ratios is a timely challenge. One of the prospective directions is a study of the interaction of benzoquinone with enaminoketones, resulting in the preparation of derivatives of 5-hydroxy-3-acyl indole and -benzofuran.

The literature gives a series of examples of the application of enaminoketones, prepared by the reaction of acetylacetone with ammonia and aliphatic and aromatic amines, in this


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