SYNTHESIS OF 1-SUBSTITUTED 6-NITRO-4-OXO-1,4-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS AS POTENTIAL ANTIMICROBIAL DRUGS

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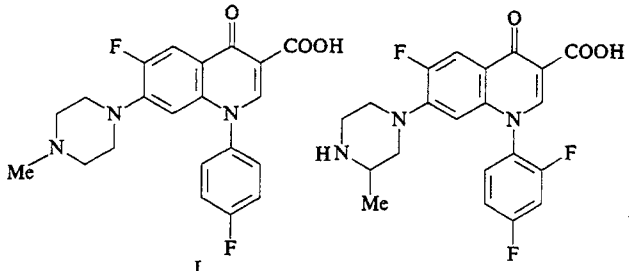
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 31, No. 5, pp. 23 – 25, May, 1997.

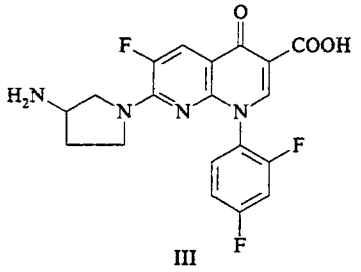
Original article submitted November 26, 1996.

Interest in 1-aryl-4-oxoquinoline-3-carboxylic acids is inspired by the fact that a series of antibacterial drugs representing the group of fluoroquinolones, such as difloxacin (I) [1], temafloxacin (II) [2], and tozufloxacin (III) [3] contain 4-fluoro- or 2,4-difluorophenyl substituents at a quinoline nitrogen atom:



I

II



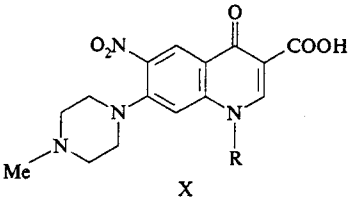
III

Within the framework of this investigation, we have obtained several derivatives of 6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid having, besides the aryl fragments, some other substituents in position 1 that account for the high antibacterial activity in the series of fluoroquinolones [4].

Ethyl esters of 3-ethoxy and 3-dimethylamino-2-(5-nitro-2,4-dichlorobenzoyl)acrylic acids (IVa, IVb) [1, 5, 6] were used as the base substance. Both compounds react under mild conditions with various anilines to form secondary enamines V. It should be noted that the reaction can be performed with the amine bases as well as with their hydrochlorides. Enamines V, sometimes not isolated as individual compounds, exhibit cyclization under the action of triethylamine with the formation of the corresponding derivatives of 4-oxoquinoline-3-carboxylic acids VI. This is followed by substituting a piperazine residue for the chlorine atom in position 7. The reaction readily proceeds on boiling compound VI with piperazine derivatives in acetonitrile in the presence of triethylamine. The resulting esters of 7-piperazinyl-4-oxoquinoline-3-carboxylic acids VII are hydrolyzed in an acid medium to obtain hydrochlorides or bases of the corresponding amino acids IX.

An alternative synthetic pathway consists in the initial hydrolysis of esters VI to the corresponding acids VIII, followed by their amination with the formation of compounds IX (see Scheme below).

A similar procedure was used to obtain derivatives of 6-nitro-4-oxoquinoline-3-carboxylic acids, containing substituents other than $R^1C_6H_4$ at the nitrogen atom of the quinoline cycle:



X

EXPERIMENTAL PART

The proposed structures of the synthesized compounds were confirmed by data of elemental analyses, mass spectrometry, and ^1H NMR spectroscopy. The elemental analyses agree with the results of analytical calculations according to the proposed formulas.

3-Arylamino-2-(5-nitro-2,4-dichlorobenzoyl)acrylic acids (V). A mixture of 12 mmole of compound IVa and 10 mmole of the corresponding aniline in 30 ml of absolute ethanol was heated with stirring for 2 h at 70 – 80°C, cooled to room temperature, and allowed to stand for 1 day in a re-

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0091-150X/97/3105-0240$18.00

frigerator. Then the precipitate was filtered, washed with 5 ml of ethanol, and dried to obtain compounds V at a 90 – 100% yield.

Ethyl esters of 1-aryl-6-nitro-4-oxo-7-chloro-1,4-dihydroquinoline-3-carboxylic acids (VI).

Method A. A mixture of 10 mmole of compound V, 3 ml (22 mmole) of triethylamine, and 30 ml of DMF was heated with stirring for 1 h at 120 – 130°C cooled to room temperature. The precipitate was filtered, washed sequentially with 20 ml of water and 5 ml of ethanol, and dried to obtain compounds VI.

Method B. A mixture of 12 mmole of compound IVa (IVb) and 10 mmole of the corresponding aniline in 30 ml of absolute ethanol was boiled for 2 – 3 h and then evaporated in vacuum. To a residue was added 3 ml (22 mmole) of triethylamine and 30 ml of DMF, and the mixture was heated with stirring for 1 h at 120 – 130°C, cooled to room temperature, and poured into 300 ml of cold water. The precipitate was filtered, washed with 5 ml of ethanol, and dried to obtain compounds VI.

Ethyl esters of 7-piperazine-substituted 1-aryl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (VII). A mixture of 10 mmole of compound VI, 50 mmole of 1- or 2-methylpiperazine, 10 ml of triethylamine, and 100 ml of acetonitrile was boiled for 3 h. Then the reaction mass was cooled to room temperature and allowed to stand for 1 day in a refrigerator. The precipitate was filtered, washed with 10 ml of acetonitrile, and dried to obtain compounds VII at a 60 – 90% yield.

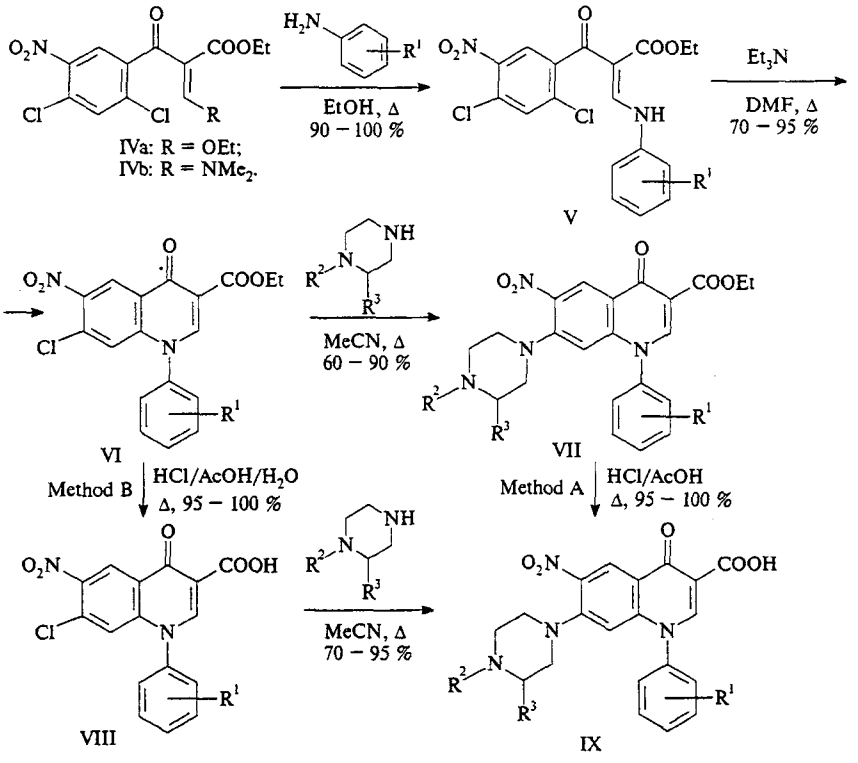
1-Aryl-6-nitro-4-oxo-7-chloro-1,4-dihydro- quinoline-3-carboxylic acids (VIII). Compound VI (25 mmole) was boiled for 3 h in 60 ml of a mixture comprising equal volumes of water, acetic acid, and concentrated hydrochloric acid. Then the mixture was cooled to room temperature and the precipitate was filtered, washed with 5 ml of ethanol, and dried to obtain compounds VIII at a 95 – 100% yield.

7-Piperazine-substituted 1-aryl-6-nitro-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (IX).

Method A. Compound VII (10 mmole) was boiled for 2 h in 60 ml of a mixture comprising equal volumes of water, acetic acid, and concentrated hydrochloric acid. Then the mixture was cooled to room temperature and and poured into 100 ml of cold water. The precipitate was filtered, washed sequentially with 30 ml of water and 10 ml of ethanol, and dried to obtain compounds IX.

Method B. A mixture of 10 mmole of compound VIII, 50 mmole of 1- or2-methylpiperazine, 10 ml of triethy-

Scheme



(substituents R^1, R^2, and R^3 are listed in Table 1).

TABLE 1. Yields and Melting Temperatures of Compounds IX

R^1	R^2	R^3	Yield, %	M.p., °C (DMF)	Empirical formula	Method
4-F	Me	H	96.2	291 – 293	$C_{21}H_{19}FN_4O_5$	B
3-F	Me	H	93.3	261 – 262	$C_{21}H_{19}FN_4O_5$	B
4-Cl	Me	H	92.7	287 – 288	$C_{21}H_{19}ClN_4O_5$	B
3-Cl	Me	H	87.0	256 – 257	$C_{21}H_{19}ClN_4O_5$	B
4-Me	Me	H	96.4	286 – 287	$C_{22}H_{22}N_4O_5$	B
3-Me	Me	H	85.8	266 – 267	$C_{22}H_{22}N_4O_5$	B
2-Me	Me	H	83.6	281 – 282	$C_{22}H_{22}N_4O_5$	B
2.6-Me_2	Me	H	86.3	282 – 283	$C_{23}H_{24}N_4O_5$	B
2.3-Me_2	Me	H	88.2	292 – 293	$C_{23}H_{24}N_4O_5$	B
2-COOH	Me	H	76.8	265 – 266	$C_{22}H_{20}N_4O_7 \cdot HCl \cdot H_2O$	A
4-MeO	Me	H	84.6	285 – 287	$C_{22}H_{22}N_4O_6$	B
4-F	H	Me	97.3	296 – 297	$C_{21}H_{19}FN_4O_5$	B
4-OH	H	Me	78.6	275 (decomp.)	$C_{21}H_{20}N_4O_6 \cdot HCl \cdot H_2O$	A
3-OH	H	Me	95.6	290 (decomp.)	$C_{21}H_{20}N_4O_6 \cdot HCl \cdot H_2O$	A
4-NO_2	H	Me	83.0	299 – 300	$C_{21}H_{19}N_5O_7 \cdot HCl \cdot 2H_2O$	A
3-NO_2	H	Me	58.0	252 – 254	$C_{21}H_{19}N_5O_7 \cdot HCl \cdot H_2O$	A
2-NO_2	H	Me	96.0	274 – 275	$C_{21}H_{19}N_5O_7 \cdot HCl \cdot H_2O$	A
2.4-$(NO_2)_2$	H	Me	89.0	> 300 (decomp.)	$C_{21}H_{18}N_6O_9 \cdot HCl \cdot H_2O$	A

TABLE 2. Yields and Melting Temperatures of Compounds X

R	Yield, %	M.p., °C (DMF)	Empirical formula	Method
NMe_2	76.0	256 – 257	$C_{17}H_{21}N_5O_5$	B
OMe	69.3	244 – 245	$C_{16}H_{18}N_4O_6$	B
NHPh	85.2	250 – 252	$C_{21}H_{21}N_5O_5$	B
NH_6H_4-F-4	86.0	229 – 231	$C_{21}H_{20}FN_5O_5$	B
$CH_2CH{=}CH_2$	68.1	264 – 266	$C_{18}H_{20}N_4O_5$	B
CH_2NMe_2	92.3	259 – 260	$C_{18}H_{23}N_5O_5$	B
CH_2CH_2OH	88.6	> 300 (decomp.)	$C_{17}H_{20}N_4O_6$	B
$CH_2CH_2NEt_2$	87.8	> 300 (decomp.)	$C_{19}H_{24}N_5O_5$	B
1-(1-Adamantyl)ethyl	90.1	245 – 246	$C_{27}H_{34}N_4O_5$	B
Furfuryl	67.8	234 – 235	$C_{20}H_{20}N_4O_6$	B
2-Cyanocyclopentyl	75.3	> 300 (decomp.)	$C_{21}H_{21}N_5O_5 \cdot HCl \cdot H_2O$	A

lamine, and 100 ml of acetonitrile was boiled for 6 h. Then the reaction mass was cooled to room temperature and allowed to stand for 1 day in a refrigerator. The precipitate was filtered, washed with 10 ml of acetonitrile, and dried to obtain compounds IX. The particular methods, yields, and melting temperatures of compounds IX are listed in Table 1.

1-Substituted 6-nitro-7-(4-methyl-1-piperazinyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acids (X). Compounds X were obtained similarly to compounds IX. The particular methods, yields, and melting temperatures of compounds X are given in Table 2.

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