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4-HYDROXY-2-QUINOLONES 141*. SYNTHESIS AND STRUCTURE OF 5R-3-HYDROXY-1,5-DIHYDRO-PYRAZOLO[4,3-*c*]QUINOLIN-4-ONES

I. V. Ukrainets[1], V. V. Kravtsova[1], A. A. Tkach[1], and G. Sim[2]

Treatment of 1R-4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines with p-toluenesulfonylhydrazide in refluxing ethanol and in the presence of triethylamine gives the 3-hydroxy-5R-1,5-dihydropyrazolo[4,3-c]quinolin-4-ones. The possible mechanism of formation, features of the steric structure of the synthesized compounds, and their NMR and mass spectra are discussed.

Keywords: 1,5-dihydropyrazolo[4,3-*c*]quinolin-4-ones, 4-chloro-2-oxo-1,2-dihydroquinolines, *p*-toluenesulfonylhydrazide, X-ray structural analysis.

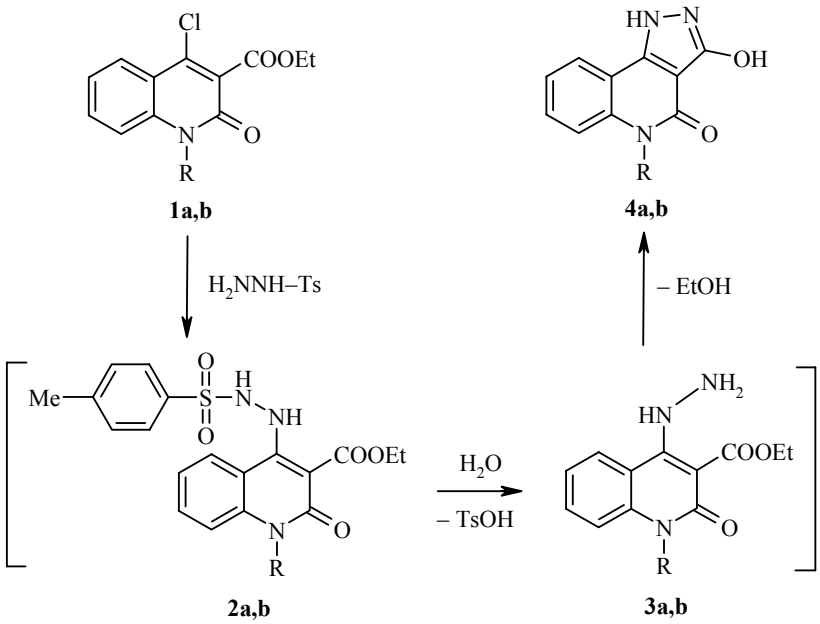
The reactions of activated hetaryl halides with *p*-toluenesulfonylhydrazide and subsequent basic hydrolysis of the intermediate β-N-hetarylhydrazides formed is generally a well known method for the exchange of halogen in a heterocycle for hydrogen [2, 3]. The yields are not always high but the simplicity of carrying out the experiment and the possibility of performing it with substances containing different reducing groups often warrants such a route.

We have previously unsuccessfully attempted to modify the 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate esters **1a,b** to the corresponding 4H-derivatives by direct reductive dehalogenation in the system zinc–glacial acetic acid [4]. At the same time we have repeatedly noted the ease with which the chlorine atom in such compounds is substituted by N-nucleophiles with a simultaneous inertness of the ester component [5-7]. It is therefore quite logical to propose an indirect method of exchanging the chlorine for hydrogen in the esters **1a,b** involving an initial synthesis of the β-N-hetaryl-substituted tosylhydrazides **2a,b** which might then be converted to the 2-oxo-1,2-dihydroquinoline-3-carboxylic acids or their ethyl esters with a standard basic hydrolysis.

It was found that the 4-chloro-substituted esters **1a,b** in refluxing 96% ethanol and in the presence of triethylamine actually quite readily reacted with *p*-toluenesulfonylhydrazide. However, the ^{1}H NMR spectra gave an unexpected result. The compounds obtained did not contain a *p*-toluenesulfonyl fragment in its structure. The ethoxycarbonyl groups which are normally stable under analogous conditions [5, 6] together with the halogen atom (negative Beilstein test) were also absent. In their place there appeared at low field two singlets, each of intensity 1H, which could be identified from their chemical shift as due to NH or OH group protons.

* For Communication 140 see [1].

[1]National University of Pharmacy, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2]Far Eastern State Medical University, Khabarovsk 680000, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 233-238, February, 2008. Original article submitted March 22, 2007.



1–4 a R = Me, **b** R = Et

An unambiguous answer to the structure of the products of the reaction of esters **1a,b** with *p*-toluenesulfonylhydrazide which was fully in agreement with the above ^{1}H NMR spectroscopic data was derived from the result of an X-ray analysis. It was shown that the compounds investigated are the 5-alkyl-substituted 3-hydroxy-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-ones **4a,b**.

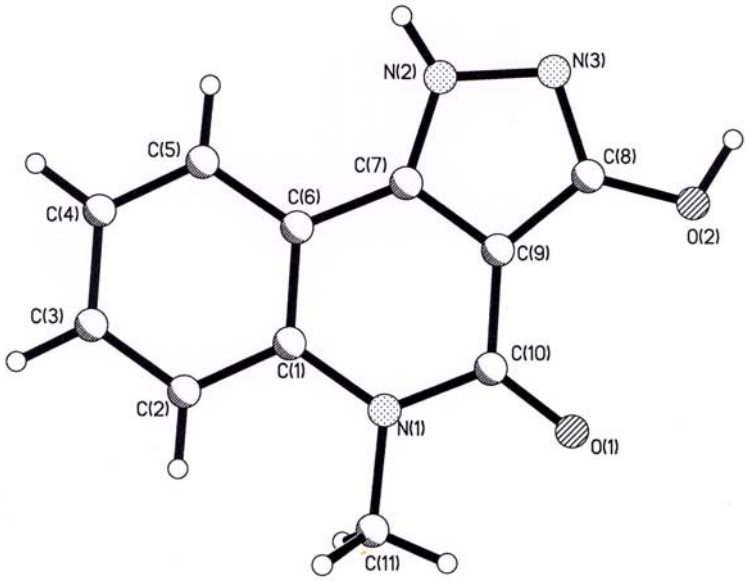


Figure 1. Structure of the 5-methylpyrazoloquinoline molecule **4a** with atomic numbering.

All of the non-hydrogen atoms in the 5-methylpyrazoloquinoline molecule **4a** lie in a single plane to within 0.03 Å (see Figure 1 and Tables 1 and 2) despite the marked repulsion between the N-methyl group, the neighboring carbonyl group, and the benzene ring atoms with shortened intramolecular contacts: $H_{(2)}\cdots C_{(11)}$ 2.48

(sum of van der Waal radii [8] 2.87), $H_{(2)}\cdots H_{(11a)}$ 2.21 (2.34), $H_{(11a)}\cdots C_{(2)}$ 2.73 (2.87), $H_{(11b)}\cdots C_{(2)}$ 2.85 (2.87), and $H_{(11c)}\cdots O_{(1)}$ 2.19 Å (2.46 Å). The formation of the intermolecular hydrogen bonds $O_{(2)}–H_{(2O)}\cdots N_{(3)}$ (-*x*, 1-*y*, 1-*z*), H···N 1.72 Å, O–H···N 177º and $N_{(2)}–H_{(2N)}\cdots O_{(1)}$ (0.5+*x*, 0.5-*y*, 0.5+*z*) H···O 1.93 Å, N–H···O 152º causes a redistribution of electron density in the molecule as a result of which the bonds $O_{(1)}–C_{(10)}$ 1.241(2), $N_{(2)}–N_{(3)}$ 1.384(2), and $C_{(7)}–C_{(9)}$ 1.385(2) Å are lengthened when compared with their mean values [9] of 1.210, 1.366, and 1.326 Å respectively and the bonds $C_{(6)}–C_{(7)}$ 1.433(2), $C_{(8)}–C_{(9))}$ 1.421(2), and $C_{(9)}–C_{(10)}$ 1.429(2) Å are shortened (mean values 1.470, 1.455, and 1.455 Å respectively).

In the crystal the pyrazoloquinoline **4a** molecules form dimers *via* a strong intermolecular hydrogen bond O–H···N. In turn, the dimers form stacs along the crystallographic (1 0 0) direction *via* an intermolecular hydrogen bond N–H···O.

The mass spectra of the pyrazoloquinolines **4a,b** are basically similar although some individual features are seen. The 5-N-methyl-substituted derivative **4a** forms a highly stable molecular ion with *m/z* 215 (100%). Fission of the molecule begins with elimination of CO and only after this is the N-methyl substituent lost while the intensity of all of the peaks of the fragment ions does not exceed 13%. Fragmentation of the 5-ethylpyrazoloquinoline **4b** occurs *via* a predominantly similar scheme. However, other routes are also possible, differing only in that they begin with elimination of the terminal methyl group.

Turning to the results of our study we briefly consider a discussion of alternative proposals for the formation of the pyrazoloquinolines **4a,b**. The first of these is based on the fact that the nucleophilic substitution of the chlorine atom in the esters **1a,b** by a *p*-toluenesulfonylhydrazide residue can indeed occur

TABLE 1. Bond Lengths (*l*) in the Pyrazoloquinoline **4a** Structure

Bond	*l*, Å	Bond	*l*, Å
$O_{(1)}–C_{(10)}$	1.241(2)	$O_{(2)}–C_{(8)}$	1.331(1)
$N_{(1)}–C_{(10)}$	1.390(2)	$N_{(1)}–C_{(1)}$	1.409(2)
$N_{(1)}–C_{(11)}$	1.463(2)	$N_{(2)}–C_{(7)}$	1.342(2)
$N_{(2)}–N_{(3)}$	1.384(2)	$N_{(3)}–C_{(8)}$	1.329(2)
$C_{(1)}–C_{(6)}$	1.407(2)	$C_{(1)}–C_{(2)}$	1.411(2)
$C_{(2)}–C_{(3)}$	1.381(2)	$C_{(3)}–C_{(4)}$	1.393(2)
$C_{(4)}–C_{(5)}$	1.381(2)	$C_{(5)}–C_{(6)}$	1.400(2)
$C_{(6)}–C_{(7)}$	1.433(2)	$C_{(7)}–C_{(9)}$	1.385(2)
$C_{(8)}–C_{(9)}$	1.421(2)	$C_{(9)}–C_{(10)}$	1.429(2)

TABLE 2. Valence Angles (ω) in the Pyrazoloquinoline **4a** Structure

Angle	ω, deg	Angle	ω, deg
$C_{(10)}–N_{(1)}–C_{(1)}$	123.7(1)	$C_{(10)}–N_{(1)}–C_{(11)}$	117.1(1)
$C_{(1)}–N_{(1)}–C_{(11)}$	119.2(1)	$C_{(7)}–N_{(2)}–N_{(3)}$	110.8(1)
$C_{(8)}–N_{(3)}–N_{(2)}$	105.7(1)	$C_{(6)}–C_{(1)}–N_{(1)}$	121.2(1)
$C_{(6)}–C_{(1)}–C_{(2)}$	118.2(1)	$N_{(1)}–C_{(1)}–C_{(2)}$	120.6(1)
$C_{(3)}–C_{(2)}–C_{(1)}$	120.1(1)	$C_{(2)}–C_{(3)}–C_{(4)}$	121.4(1)
$C_{(5)}–C_{(4)}–C_{(3)}$	119.5(1)	$C_{(4)}–C_{(5)}–C_{(6)}$	120.1(1)
$C_{(5)}–C_{(6)}–C_{(1)}$	120.9(1)	$C_{(5)}–C_{(6)}–C_{(7)}$	123.4(1)
$C_{(1)}–C_{(6)}–C_{(7)}$	115.8(1)	$N_{(2)}–C_{(7)}–C_{(9)}$	108.1(1)
$N_{(2)}–C_{(7)}–C_{(6)}$	130.0(1)	$C_{(9)}–C_{(7)}–C_{(6)}$	121.9(1)
$N_{(3)}–C_{(8)}–O_{(2)}$	122.8(1)	$N_{(3)}–C_{(8)}–C_{(9)}$	110.7(1)
$O_{(2)}–C_{(8)}–C_{(9)}$	126.5(1)	$C_{(7)}–C_{(9)}–C_{(8)}$	104.7(1)
$C_{(7)}–C_{(9)}–C_{(10)}$	122.4(1)	$C_{(8)}–C_{(9)}–C_{(10)}$	132.9(1)
$O_{(1)}–C_{(10)}–N_{(1)}$	120.8(1)	$O_{(1)}–C_{(10)}–C_{(9)}$	124.2(1)
$N_{(1)}–C_{(10)}–C_{(9)}$	115.0(1)		

under the conditions of the studied reaction. In such a case further chemical transformation of the intermediate β-N-hetaryl-substituted tosyl hydrazides **2a,b**, although being possible, is considerably unexpected. The basis for this conclusion is that β-N-hetarylhydrazides of aromatic sulfonic acids are generally stable compounds. Their decomposition needs quite rigid conditions and requires the presence of base [2, 3]. In our example of the tosyl hydrazides **2a,b** (if they are formed indeed) they are hydrolyzed unusually readily and in virtually neutral medium since the added equivalent of triethylamine would be combined with the hydrogen chloride evolved. In addition, the mechanism of the base induced decomposition of arylsulfonylhydrazines, studied in detail in many examples of the practically analogous McFayden-Stevens reaction [10], does not include a stage of substituted hydrazine formation. Hence the formation of the hydrazinoquinolines **3a,b** as synthetic precursors of the pyrazoloquinolines **4a,b** can only be considered as the result of hydrolysis of the tosylhydrazides **2a,b** under neutral conditions. It must be emphasized that the formation of the hydrazinoquinolines **3a,b** is probably a necessary condition for subsequent heterocyclization. Otherwise its realization *via* removal of the protecting group involving the rather low reactivity ethoxycarbonyl groups in ethyl 4-amino-substituted 2-oxo-1,2-dihydroquinoline-3-carboxylates [5-7] is unlikely.

The basis of the second possible route for formation of the pyrazoloquinolines **4a,b** lies in the proposal that formation of the tosyl hydrazides **2a,b** is not essential overall. Hence, for example, the ability of *p*-toluenesulfonyl hydrazide to decompose slowly to hydrazine when refluxed in ethanol has been known for a long time [2]. Its subsequent reaction with 4-chloro esters **1a,b**, in turn leading to the hydrazinoquinolines **3a,b** and then inevitably to closure of the pyrazole ring is quite obvious and predictable and does not need additional explanation.

EXPERIMENTAL

The ^{1}H NMR spectra of the pyrazoloquinolines **4a,b** were recorded on a Varian Mercury VX-200 instrument (200 MHz) using DMSO-d_6 solvent and TMS internal standard. Mass spectra were taken on a Varian 1200L spectrometer with full scanning in the range 35-700 *m/z*, electron impact ionization 70 eV, and with direct introduction. Commercial p-toluenesulfonylhydrazide from the Aldrich Company was used in the work.

3-Hydroxy-5-methyl-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-one (4a). A solution of the 4-chloro-substituted ester **1a** (2.65 g, 0.01 mol), *p*-toluenesulfonylhydrazide (1.86 g, 0.01 mol), triethylamine (1.4 ml, 0.01 mol), and ethanol (30 ml) was refluxed for 15 h. The reaction mixture was cooled and the precipitate formed was filtered off, washed with cold alcohol and dried. Yield 1.63 g (76%); mp 353-355ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.92 (1H, s, NH); 10.81 (1H, s, OH); 8.00 (1H, dd, *J* = 7.7 and 1.4, H-9); 7.56 (1H, td, *J* = 7.6 and 1.4, H-7); 7.46 (1H, d, *J* = 8.7, H-6); 7.27 (1H, td, *J* = 7.5 and 1.4, H-8); 3.54 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 215 $[M]^+$ (100), 187 $[M\text{-}CO]^+$ (5), 172 $[M–CO–CH_3]^+$ (5), 158 $[M–CO–CHO]^+$ (13). Found, %: C 61.48; H 4.35; N 19.46. $C_{11}H_9N_3O_2$. Calculated, %: C 61.39; H 4.22; N 19.52

5-Ethyl-3-hydroxy-1,5-dihydropyrazolo[4,3-*c*]quinolin-4-one (5b) was prepared by the method of synthesis of pyrazoloquinoline **4a**. Yield 1.67 g (73%); mp 336-338ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.92 (1H, s, NH); 10.67 (1H, s, OH); 8.02 (1H, d, *J* = 7.5, H-9); 7.57-7.49 (2H, m, H-6,7); 7.26 (1H, t, *J* = 7.0, H-8); 4.23 (2H, q, *J* = 7.0, NCH_2); 1.16 (3H, t, *J* = 7.0, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 229 $[M]^+$ (100), 214 $[M\text{-}CH_3]^+$ (29), 201 $[M–CO]^+$ (50), 186 $[M–CH_3–CO]^+$ (8), 172 $[M–CO–CHO]^+$ (16), 157 $[M–CH_3–CO–CHO]^+$ (9). Found, %: C 62.93; H 4.77; N 18.28. $C_{12}H_{11}N_3O_2$. Calculated, %: C 62.87; H 4.84; N 18.33.

X-ray structural Investigation. Crystals of the pyrazoloquinoline **4a** are monoclinic (DMF), at -173ºC: *a* = 6.954(1), *b* = 10.634(1), *c* = 13.236(5) Å, β = 101.11(2)º, *V* = 960.4(4) Å^3, M_r = 215.21, *Z* = 4, space group $P2_1/n$, d_{calc} = 1.488 g/cm^3, μ(MoKα) = 0.107 mm^{-1}, *F*(000) = 448. The unit cell parameters and intensities of 5646 reflections (2170 independent with R_{int} = 0.019) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 55º).

The structure was solved by a direct method using the SHELXTL program package [11]. The positions of the hydrogen atoms were revealed in electron density difference synthesis and refined isotropically. The structure was refined by F_2 full matrix-least squares analysis in the anisotropic approximation for non-hydrogen atoms to $wR_2 = 0.092$ for 2160 reflections ($R_1 = 0.035$ for 1571 reflections with $F > 4\sigma(F)$, $S = 0.993$). The full crystallographic information has been placed in the Cambridge structural data base (reference CCDC 650 597). Interatomic distances and valence angles are given in Tables 1 and 2.

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