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4-HYDROXY-2-QUINOLONES 147*. SYNTHESIS AND TAUTOMERISM OF 2-METHYL-9H-FURO-[2,3-*b*]QUINOLIN-4-ONE

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In the presence of aqueous solutions of alkali, 2-bromomethyl-3,9-dihydro-2H-furo[2,3-b]quinolin-4-one is subjected to dehydrobromination and converted to 2-methyl-9H-furo[2,3-b]quinolin-4-one which exists in acid solution in the 4-oxo- and in base in the 4-hydroxy tautomeric forms.

Keywords: furo[2,3-*b*]quinoline, dehydrobromination, tautomerism

Furo[2,3-*b*]quinoline alkaloids are widely found in nature. They are most often discovered and separated from numerous forms of the *Rutaceae* plant family [2-7]. Complex preparations based on furoquinoline-containing plant materials have been used for a long time in natural and state medicines as anti-spasmodic [8], antiHIV [9], antifungal [10], cytotoxic [11], and antimicrobial [12] agents. Medicines of this type are generally standardized through the content of one or two basic components but sometimes through the overall content of all of the alkaloids. At the same time, the effect on man of each component individually is far from well known and, in the end, this negatively effects the efficiency and safety of the medical treatment. Hence more complete investigations have often appeared in recent times directed to a study of the biological properties not of natural mixtures but specifically towards a particular furoquinoline alkaloid. As a result, γ-fagarine has proved to be a powerful inhibitor of human phosphodiesterase V [13], skimmianine a 5-hydroxy-tryptamine (5-HT) receptor inhibitor in animals [14], and confusameline a trombocite aggregation ihibitor [15], dictamnine a powerful mutagen towards *Salmonella typhimurium* [16]. Acronidine has revealed antimalarial [17] and HA-7 (N-benzyl-7-methoxy-2,3,4,9-tetrahydrofuro[2,3-*b*]quinoline-3,4-dione) anti-arrhythmic [18] effects.

At the same time the separation of individual alkaloids from plants is frequently a rather labor intensive process. Hence in this case it is particularly timely to use organic synthesis which allows the preparation not only of natural compounds but of their modified analogs. Two principally different schemes are known for building up a furo[2,3-*b*]quinoline system. The first includes the initial preparation of furan intermediates after which the quinoline fragment is added on [19, 20]. The second is more frequently used and involves the

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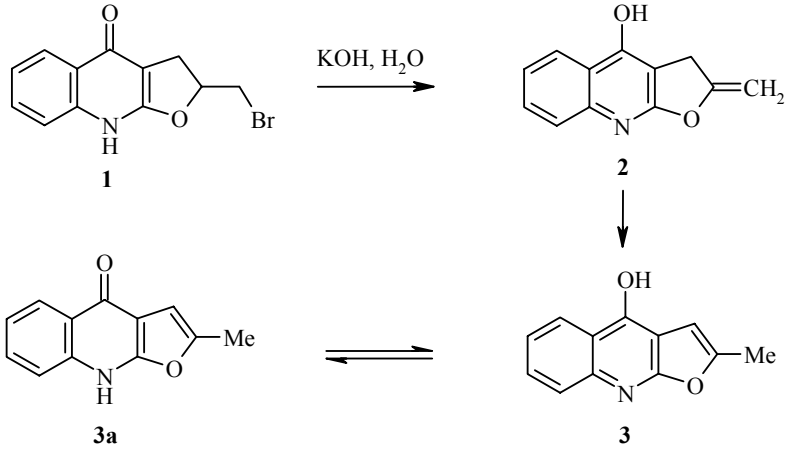
formation of a furan ring from 3-substituted quinol-2-ones [21, 22]. Such a route was, in fact, used by us in the synthesis of 2-bromomethyl-2,3-dihydro-9H-furo[2,3-*b*]quinolin-4-one (**1**) in high yield *via* bromination of 3-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline using molecular bromine [23].

Treatment of similarly structured 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinolines with aqueous solutions of alkali metal hydroxides results in hydrolysis of the oxazole ring and occurs *via* intermediate 2-methylene derivatives which can be separated and characterized as needed [24]. By contrast the furan ring in 2-bromomethylfuroquinoline **1** is not opened under analogous conditions. According to chromato-mass spectrometric data it only affects the side bromomethyl group undergoing dehydrobromination and forms a single substance with molecular mass 199 amu in the final step. The absence of a peak characteristic of the ion $[M\text{-}CH_3]^+$ in the methyl-substituted compounds allows us to suggest that the sample studied is the 2-methylenefuroquinoline **2**. However, the ^{1}H NMR spectrum unambiguously shows the presence of a methyl and not methylene group. Hence the compound obtained exists as the aromatic 2-methyl-substituted tautomer **3**.



In order to make a more detailed proof of the structure of the compound synthesized we have recorded its ^{1}H and ^{13}C NMR spectra and also carried out heteronuclear ^{1}H-^{13}C correlation experiments. It was found that the signals for the proton spectrum measured in DMSO were mostly strongly broadened and this is likely a result of the presence of a tautomeric equilibrium **3** ↔ **3a** in the ratio ~ 1:1 in the molecule and in which the 4-OH group partially migrates to the heterocyclic nitrogen atom. This feature does not permit a heteronuclear correlation study in DMSO.

Trifluoroacetic acid proved to be a more suitable solvent for this task. Even though the NH and OH group proton signals were absent due to rapid deuterium exchange the tautomerism mentioned above did not occur since the strongly acidic medium shifted the equilibrium to the more basic NH form **3a**. The spectrum showed two doublets and two triplets for the aromatic system of the 1,2-disubstituted benzene ring as well as singlets for the methyl group and for another aromatic proton. All of this forms the basis that the compound studied in trifluoroacetic acid solution is 2-methyl-9H-furo[2,3-*b*]quinolin-4-one (**3a**). Table 1 gives the heteronuclear correlations found through one (HMQC spectra) or through 2 or 3 (HMBC) chemical bonds. The data obtained also allows the assignment of all of the signals in the carbon spectrum which confirms the conclusion made. The assignment of the signals of the proton-bearing carbon atoms is made from the HMQC spectrum and the signals for the quaternary carbon atoms can be assigned from the presence of further correlations in the HMBC spectrum. It was interesting to note that correlations through four chemical bonds were seen for several protons in the HMQC spectrum. In particular there is a *W*-type correlation interaction between the 2-methyl group and the C-3a atom absorbing at 108.9 ppm and also between the H-8 proton with a chemical shift of 8.04 ppm and the carbonyl C-4 atom seen at 163.5 ppm. Weak correlations are also seen for a

series of protons in the aromatic ring with the corresponding carbon atoms. The scheme below gives the assignments of signals in the proton and carbon spectra of the structure studied with the important HMBC correlations which served as the basis for these assignments.

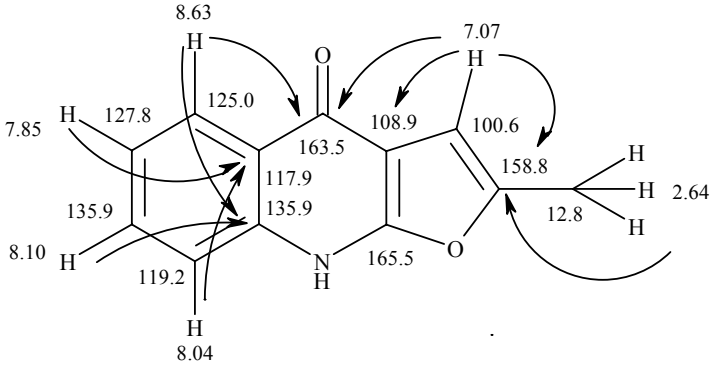


TABLE 1. Heteronuclear $^{1}H–^{13}C$ Correlations for the 2-Methylfuro-quinoline **3a**

δ, ppm	HMQC	HMBC
8.63	125.0	163.5; 135.9; 119.2 (*w*); 117.9
8.10	135.9	135.9; 125.0; 117.9
8.04	119.2	127.8; 117.9; 163.5 (*w*)
7.85	127.8	135.9; 125.0; 119.2; 117.9
7.07	100.6	158.8; 108.9; 163.5
2.64	12.8	158.8; 108.9 (*w*); 100.6

As is seen in the scheme the signals for all of the carbon atoms have a chemical shift which agrees with their positioning in the molecule. Fusion of the furan ring with the 4-quinolone fragment follows from the presence in the HMBC spectrum of a correlation for the carbonyl C-4 atom absorbing at 163.5 ppm with the furan H-3 proton at 7.07 ppm on the one side and with the quinolone H-5 proton signal at 8.63 ppm on the other.

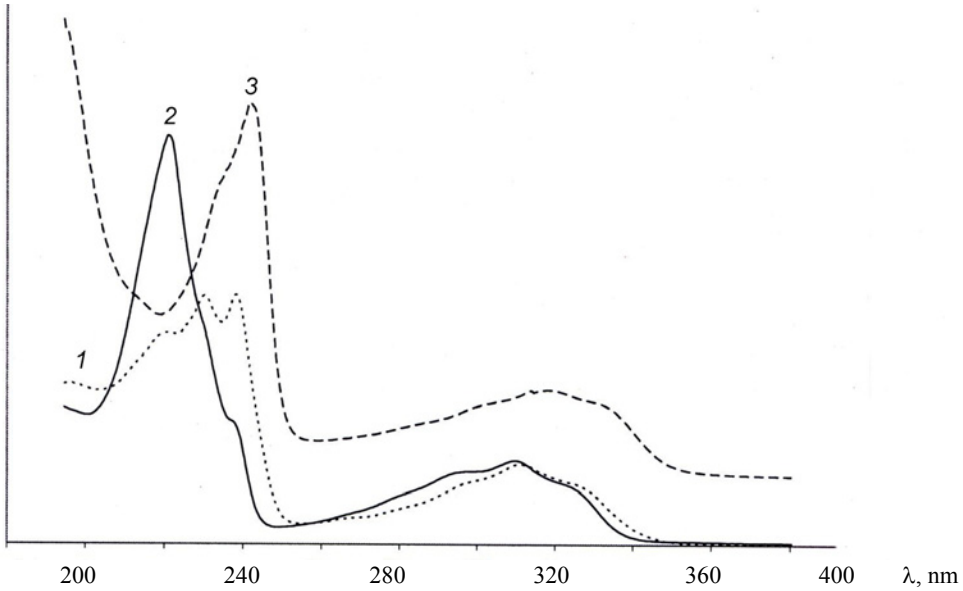


Fig. 1. Correlated UV spectra of 2-methylfuroquinoline **3**: *1* - in ethanol; *2* – with addition of HCl; *3* – with addition of KOH

The existence of the synthesized 2-methyl-9H-furo[2,3-*b*]quinolin-4-one in neutral solvents as two tautomers is graphically illustrated by UV spectrophotometry (Fig. 1). The spectrum recorded in ethanol is shown superimposed on those recorded separately in acid (4-oxo form **3a**) and basic (4-hydroxy form **3**) media.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra of the 2-methylfuroquinoline **3**, the 2D COSY ^{1}H NMR experiments, and the HMQC and HMBC heteronuclear correlation spectra were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All of the 2D experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequences were respectively $^{1}J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The numbers of increments in the COSY and HMQC spectra were 128 and in the HMBC spectra 400. In all cases CF_3CO_2D was used as solvent and TMS as internal standard. The chromato-mass spectrum was recorded in full scanning mode in the range *m/z* 35-700 on a Hewlett Packard 5890/5972 instrument with 70 eV electron impact ionization. The Hewlett Packard-5MS chromatographic column was of length 25 m, internal diameter 0.2 mm, polysiloxane stationary phase (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm, and the gas carrier was helium. UV spectra were taken on a Specord M-40 spectrometer.

2-Methyl-9H-furo[2,3-*b*]quinolin-4-one (3a). A mixture of 2-bromomethyl-2,3-dihydro-9H-furo-[2,3-*b*]quinolin-4-one (**1)** (2.80 g, 0.01 mol) (or the corresponding amount of its hydrobromide [23]) and a 10% aqueous solution of KOH (20 ml) was refluxed for 2 h. The reaction mixture was cooled and acidified to pH 6 with HCl. The precipitate was filtered off, washed with cold water, and dried. Yield 1.69 g (85%). Mp 282-284ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.63 (1H, d, *J* = 8.0, H-5); 8.10 (1H, t, *J* = 7.6, H-7); 8.04 (1H, d, *J* = 7.8, H-8); 7.85 (1H, t, *J* = 7.7, H-6); 7.07 (1H, s, H-3); 2.64 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 165.5 (C-9a), 163.5 (C=O), 158.8 (C-2), 135.9 (C-7 + C-8a), 127.8 (C-6), 125.0 (C-5), 119.2 (C-8), 117.9 (C-4a), 108.9 (C-3a), 100.6 (C-3), 12.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 199 $[M]^+$ (100), 198 $[M\text{-}H]^+$ (46), 170 $[M\text{-}HCO]^+$ (21), 128 (63). Found, %: C 72.42; H 4.63; N 7.10. $C_{12}H_9NO_2$. Calculated, %: C 72.35; H 4.55; N 7.03.

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