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4-HYDROXY-2-QUINOLONES. 169*. SYNTHESIS AND BROMINATION OF 1-ALLYL-3-(ARYLAMINO-METHYLENE)QUINOLINE-2,4-(1H,3H)-DIONES

I. V. Ukrainets[1], Liu Yangyang[1], N. L. Bereznyakova[1], and A. V. Turov[2]**

Bromination of 1-allyl-substituted 3-(arylaminomethylene)quinoline-2,4-(1H,3H)-diones with one equivalent of molecular bromine in glacial acetic acid and subsequent dilution of the reaction mixture with water is accompanied by halocyclization and hydrolysis to form 2-bromomethyl-5-oxo-1,2 dihydro-5H-oxazolo[3,2-a]quinoline-4-carbaldehyde.

Keywords: 1-allyl-3-(arylaminomethylene)quinoline-2,4-(1H,3H)-diones, 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde, enamines, oxazolo[3,2-a]quinolines, Schiff bases, bromination, halocyclization.

As we have shown previously Schiff bases obtained by reaction of 1R-4-hydroxy-2-oxo-1,2 dihydroquinoline-3-carbaldehydes with anilines exist exclusively in the enamine tautomer form. The 3-(arylaminomethylene)quinoline-2,4-(1H,3H)-diones synthesized in this way do not react with thioglycolic acid and its esters. It was concluded that they were unable to form azomethines, i.e. 4-hydroxy-2-oxo- or 2-hydroxy-4-oxo forms [2]. In fact, this structural feature served as the reason for its involvement in the scope of our work on the bromination of *ortho*-allyl-substituted oxoheterocycles [3-7] and 1-allyl-3-(aryl-aminomethylene)quinoline-2,4-(1H,3H)-diones **1a,b**. Their preparation used the tested [8] synthetic scheme of ester **2** → hydrazide **3** → β-N-tosylhydrazide **4** → aldehyde **5** → enamines **1**. It should be noted that an alternative method including fusion of equimolar amounts of ester **2** and *p*-toluenesulfonylhydrazide at 140ºC proved unacceptable. In this case the tendency for decomposition of the *p*-toluenesulfonylhydrazide affected not only the yield of the final product but also its composition. Along with the target 1-allyl derivative **4** there was formed the 1-propyl analog **6**, the ratio of the β-N-tosylhydrazides **4** and **6** in the reaction mixture being 1:1 from ^{1}H NMR spectroscopy. Under the indicted conditions it was clear that a significant part of the *p*-tolylsulfonylhydrazide decomposed with evolution of diimide [9, 10] which, correspondingly, was actually responsible for partial reduction of the allyl double bond.

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* For Communication 168 see [1].

** To whom correspondence should be addressed, e-mail: uiv@kharkov.ua.

[1]National University of Pharmacy, Kharkiv 61002, Ukraine.
[2]Taras Shevchenko National University, Kiev 01033, Ukraine, e-mail: nmrlab@univ.kiev.ua.

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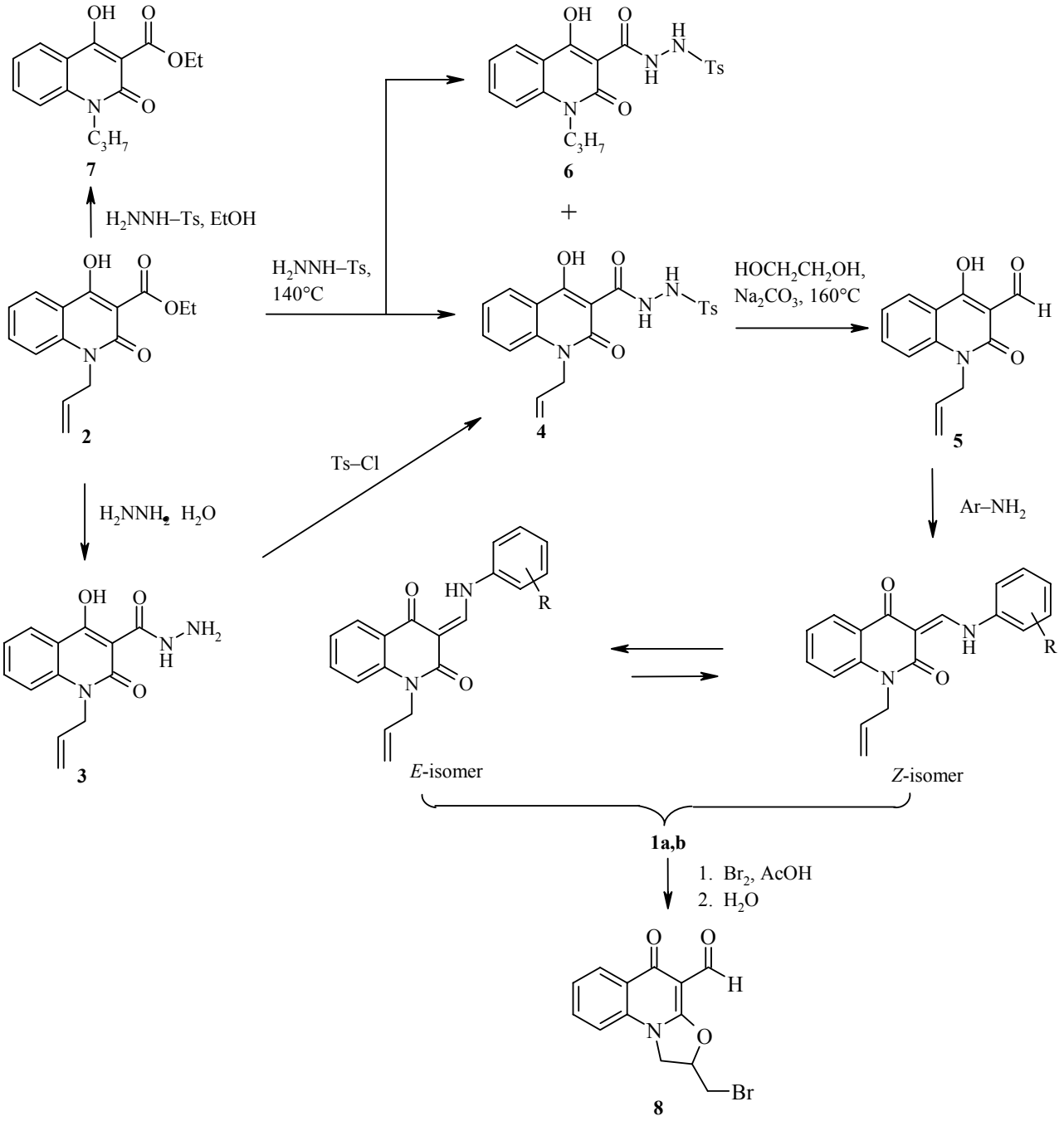
The same process also occurs under milder conditions, e.g. in refluxing ethanol, the only difference being that the carbethoxy group of ester **2** is not affected overall but the N-allyl fragment is reduced to propyl by 78% with the same equimolar ratio of reagents. Most of all, introduction of a small amount of *p*-toluenesulfonylhydrazide as source of diimide can achieve a 100% conversion of ester **2** to 3-ethoxycarbonyl-4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline [**7**]. Reactions of this type were, however, outside the terms of our investigation and were not investigated further.



1 a R = 2-MeO-5-Cl, **b** R = 4-Br

The 1-allyl-substituted 3-(arylaminomethylene)quinoline-2,4-(1H,3H)-diones **1a,b** are formed in good yields and are light yellow materials existing (at least in DMSO-d_6) as the two geometric *E*- and *Z*- isomers with a marked predominance of the former (see Experimental section). As in the case of 4-hydroxy-2-quinolones, their bromination by molecular bromine in glacial acetic acid occurs very readily, the brown color of the bromine disappearing almost instantly. It was interesting that dilution of both reaction mixtures gives the same product in which the aniline fragment was absent (according to the ^{1}H NMR spectrum). The mass spectrum supported this conclusion, pointing to the presence in the compound formed of only one bromine atom which can be the result of a later halocyclization.

For a convincing confirmation of the structure of the compound formed we have carried out heteronuclear ^{1}H–^{13}C correlation experiments and also a NOESY experiment. Although the proton spectrum of the sample analyzed shows the presence of a signal at 10.11 pm, the chemical shift of which is typical of an aldehyde proton, the ^{13}C NMR spectrum signal for the carbon atom bound to this atom appears at 186.1 ppm which is somewhat less than might be anticipated for the carbonyl group of an aldehyde fragment. Hence a reliable decision regarding the structure of the molecule could only be made on the basis of heteronuclear correlation through one (HMQC method) or through 2-3 (HMBC method) chemical bonds. Table 1 shows the cross peak coordinates seen in the corresponding 2D spectra.

Revealing the cross peaks allowed the identification of all of the carbon signals. The assignments made in this way are given in the Scheme below. The presence of an oxazolidine fragment annelated to the quinoline ring in the molecule is confirmed by the presence of cross peaks between the bridging C-3a atom with chemical

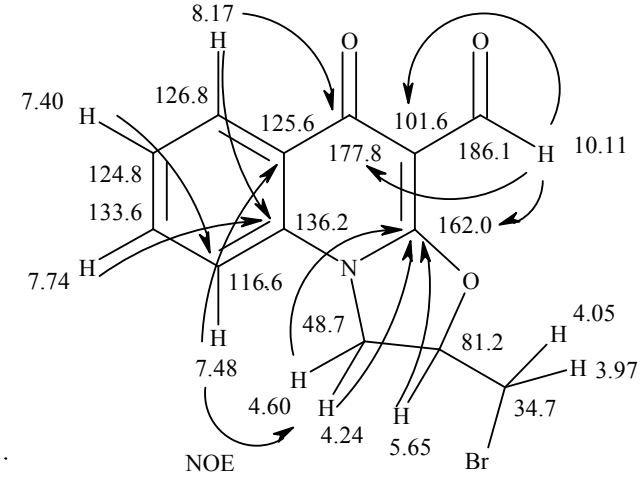


TABLE 1. Full Listing of Heteronuclear ^{1}H–^{13}C Correlations Found for the Oxazoloquinoline **8**

^{1}H signal, δ, ppm	Position of cross peaks in the ^{13}C measurement ^{13}C	
	HMQC	HMBC
10.11	186.1	162.0; 101.6; 177.8
8.17	126.8	177.8; 136.2; 133.6
7.74	133.6	136.2; 126.8
7.48	116.6	177.8; 133.6; 125.6; 124.8
7.40	124.8	177.8; 133.6; 125.6; 116.6
5.65	81.2	162.0; 34.7
4.60	48.7	162.0; 81.2; 34.7
4.24	48.7	162.0; 81.2; 34.7
4.05	34.7	48.7; 81.2
3.97	34.7	48.7; 81.2

shift of 162.0 ppm and the proton signals for the N–CH_2 methylene group and also the signal for the H-2 proton positioned next to the heterocyclic oxygen atom. The localization of the aldehyde group was confirmed by cross peaks found for the aldehyde proton and the neighboring C-3a, C-4, and C-5 atoms. Extremely suggestive in terms of the molecular structure is the chemical shift of the C-4 atom at 101.6 ppm, being close to the position of the signal for this atom in compounds with a related chemical structure [3-6].

The NOESY experiment showed that the signals for 1-CH methylene group located at 4.60 and 4.24 ppm show a strong NOE with the aromatic protons signal at 7.48 pm. This infers that the given protons are close together in space and hence the oxazolidine ring is annelated to the quinolone ring along the *a* edge such that the studied compound is 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carbaldehyde (**8**).

Dilution of the reaction mixture with water was carried out after the starting enamines **1a,b** had reacted with bromine. It therefore follows that heterocyclization clearly preceded hydrolysis. Other questions connected with the processes appearing in our investigation remain open for now. None the less, the experimental data obtained currently allows us to establish unambiguously that bromination of the 1-allyl-3-(arylamino-methylene)quinoline-2,4-(1H,3H)-diones occurs *via* halocyclization to give oxazolo[3,2-*a*]quinolines.

EXPERIMENTAL

^{1}H and ^{13}C NMR Spectra for the oxazoloquinoline **8**, ^{1}H COSY NMR 2D spectroscopic experiments, homonuclear Overhauser NOESY-2D, and also heteronuclear HMQC and HMBC experiments were recorded on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All 2D experiments were carried out with gradient selection of useful signals. Mixing times in the pulse sequences were $^1J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The number of increments in the COSY and HMQC spectra was 128 and 400 in the HMBC spectra. The mixing time in the NOESY-2D experiment was 500 ms. The ^{1}H NMR spectra of the remaining compounds were recorded on a Varian Mercury-VX-200 instrument (200 MHz). In all cases the solvent was DMSO-d_6 with TMS as internal standard. The mass spectrum of the oxazoloquinoline **8** was recorded on a Varian 1200L instrument in full scanning mode in the range 35-700 m/z, 70 eV electron impact ionization, and direct sample introduction. The synthesis and properties of 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydrazide (**3**) are given in [11].

1-Allyl-3-(5-chloro-2-methoxyphenylaminomethylene)quinoline-2,4-(1H,3H)-dione (1a). 5-Chloro-2-methoxyaniline (1.57 g, 0.01 mol) was added to a solution of 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.29 g, 0.01 mmol) in dry xylene (25 ml) and refluxed for 5 h distilling off the water formed as an azeotrope with the xylene. The reaction mixture was cooled, diluted with hexane, and left in a freezer for several hours. The light-yellow precipitate of enamine **1a** formed was filtered off, washed with hexane, and dried. Yield 3.12 g (85%); mp 163-165ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.95 (0.61H, d, *J* = 13.4, NH *E*-isomer); 12.92 (0.31H, d, *J* = 13.8, NH *Z*-isomer); 8.99 (0.66H, d, *J* = 13.4, =CH *E*-isomer); 8.95 (0.34H, d, *J* = 13.8, =CH *Z*-isomer); 8.08 (1H, dd, *J* = 7.8 and 1.2, H-5); 7.91 (0.66H, d, *J* = 2.1, H-6' *E*-isomer); 7.86 (0.34H, d, *J* = 2.1, H-6' *Z*-isomer); 7.60 (1H, td, *J* = 7.7 and 1.5, H-7); 7.33-7.12 (4H, m, H-6,8,3',4'); 5.91 (1H, m, C<u>H</u>=CH_2); 5.11 (1H, d, *J* = 10.7, NCH_2CH=C<u>H</u> *cis*); 5.04 (1H, d, *J* = 18.0, NCH_2CH=C<u>H</u> *trans*); 4.78 (2H, s, NCH_2); 3.95 (1.98H, s, OCH_3 *E*-isomer); 3.91 (1.02H, s, OCH_3 *Z*-isomer). Found, %: C 65.22; H 4.78; N 7.71. $C_{20}H_{17}ClN_2O_3$. Calculated, %: C 65.13; H 4.65; N 7.60.

1-Allyl-3-(4-bromophenylaminomethylene)quinoline-2,4-(1H,3H)-dione (1b) was prepared using the method reported above. Yield 3.56 g (93%); mp 168-170ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.73 (0.53H, d, *J* = 12.8, NH *E*-isomer); 12.65 (0.28H, d, *J* = 13.4, NH *Z*-isomer); 8.91 (0.61H, d, *J* = 12.8, =CH *E*-isomer); 8.86 (0.39H, d, *J* = 13.4, =CH *Z*-isomer); 8.08 (1H, dd, *J* = 7.9 and 1.5, H-5); 7.68-7.52 (5H, m, N-7,2',3',5',6'); 7.28 (1H, d, *J* = 8.2, H-8); 7.19 (1H, t, *J* = 7.5, H-6); 5.92 (1H, m, C<u>H</u>=CH_2); 5.14 (1H, d, *J* = 10.9, NCH_2CH=C<u>H</u> *cis*); 5.06 (1H, d, *J* = 18.1, NCH_2CH=C<u>H</u> *trans*); 4.79 (2H, s, NCH_2). Found, %: C 59.69; H 4.06; N 7.23. $C_{19}H_{15}BrN_2O_2$. Calculated, %; C 59.55; H 3.95; N 7.31.

1-Allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid β-N-Tosylhydrazide (4). Triethylamine (1.54 ml, 0.011 mol) was added to a solution of hydrazide **3** (2.59 g, 0.01 mol) in dry DMF (20 ml) followed, with stirring, by *p*-toluenesulfonyl chloride (2.1 g, 0.011 mol). The product was left for 10-12 h at room temperature and the reaction mixture was then diluted with cold water and acidified with dilute HCl to pH 5. The precipitated β-N-tosylhydrazide **4** was filtered off, washed with water, and dried. Yield 4.00 g (97%); mp 177-179ºC (DMF-ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.75 (1H, br. s, OH); 11.54 (H, s, CONH); 10.30 (1H, br. s, SO_2NH); 8.06 (1H, dd, *J* = 7.8 and 1.5, H-5); 7.79 (1H, td, *J* = 7.9 and 1.5, H-7); 7.73 (2H, d, *J* = 8.3, H-2',6'); 7.52 (1H, d, *J* = 8.5, H-8); 7.40 (2H, d, *J* = 8.3, H-3',5'); 7.36 (1H, t, *J* = 7.8, H-6); 5.91 (1H, m, C<u>H</u>=CH_2); 5.13 (1H, dd, *J* = 10.6 and 1.1, NCH_2CH=C<u>H</u> *cis*); 4.97 (1H, dd, *J* = 17.2 and 1.1, NCH_2CH=C<u>H</u> *trans*); 4.86 (2H, m, NCH_2); 2.38 (3H, s, Ar–CH_3). Found, %: C 58.25; H 4.76; N 10.05. $C_{20}H_{19}N_3O_5S$. Calculated, %: C 58.10; H 4.63; N 10.16.

1-Allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (5). Anhydrous Na_2CO_3 (3.18 g, 0.03 mol) was added in one portion to a solution of β-N-tosylhydrazide **4** (4.13 g, 0.01 mol) in ethylene glycol (20 ml) heated to 160ºC. (Caution, frothing!) Evolution of gas ceased after several minutes. The reaction mixture was cooled, diluted with water, and acidified with HCl (1:1) to pH ~ 4. The precipitated aldehyde **5** was filtered off, washed with cold water, and dried. Yield 2.15 g (94%); mp 84-86ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.08 (1H, s, CHO); 8.09 (1H, dd, *J* = 8.0 and 1.3, H-5); 7.78 (1H, td, *J* = 7.9 and 1.5, H-7); 7.46 (1H, d, *J* = 8.5, H-8); 7.33 (1H, t, *J* = 7.6 and 1.1, H-6); 5.92 (1H, m, C<u>H</u>=CH_2); 5.13 (1H, dd, *J* = 10.4 and 1.3, NCH_2CH=C<u>H</u> *cis*); 5.02 (1H, dd, *J* = 17.4 and 1.3, NCH_2CH=C<u>H</u> *trans*); 4.85 (2H, m, NCH_2). Found, %: C 68.23; H 4.95; N 5.98. $C_{13}H_{11}NO_3$. Calculated, %: C 68.11; H 4.84; N 6.11.

2-Bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carbaldehyde (8). A solution of bromine (0.52 ml, 0.01 mol) in glacial acetic acid (5 ml) was added with vigorous stirring to a solution of the quinoline-2,4-dione **1a** (3.68 g, 0.01 mol) in the same solvent (30 ml). The decolorization of the bromine was virtually instantaneous. The reaction mixture was diluted with cold water and left for 12-14 h at room temperature. The precipitated oxazoloquinoline **8** was filtered off, washed with water, and dried. Yield 1.87 g (61%). When using the quinoline-2.4-dione **1b** as starting material the yield was 57%. Mp 231-233ºC (ethanol). ^{1}H NMR spectrum,δ, ppm (*J*, Hz): 10.11 (1H, s, CHO); 8.17 (1H, dd, *J* = 8.0 and 1.4, H-6); 7.74 (1H, td, *J* = 7.8 and 1.6, H-8); 7.48 (1H, d, *J* = 8.1, H-9); 7.40 (1H, td, *J* = 7.4 and 1.2, H-7); 5.65 (1H, m, NCH_2C<u>H</u>O); 4.60 (1H, dd, *J* = 9.8 and 9.8, NCH); 4.24 (1H, dd, *J* = 9.8 and 6.6, NCH); 4.05 (1H, dd, *J* = 11.0 and 4.4, CHBr); 3.97 (1H, dd, *J* = 11.0 and 4.0, CHBr). ^{13}C NMR spectrum, δ, ppm: 186.1 (CHO); 177.8 (5-C=O); 162.0 (C-3a); 136.2 (C-9a); 133.6 (C-8); 126.8 (C-6); 124.8 (C-7); 125.6 (C-5a); 116.6 (C-9); 101.6 (C-4); 81.2 (NCH_2<u>C</u>H); 48.7 (NCH_2); 34.7 (CH_2Br). Mass spectrum, *m/z* (I_{rel}, %): 309/307 $[M]^+$ (7.6/8.2), 281/279 $[M\text{-}CHO]^+$ (100.0/79.4), 199 $[M\text{-}CHO\text{-}HBr]^+$ (5.8). Found, %: C 50.33; H 3.39; N 4.66. $C_{13}H_{10}BrNO_3$. Calculated, %: C 50.67; H 3.27; N 4.55.

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