Chemistry of Heterocyclic Compounds, Vol. 46, No. 4, 2010

4-HYDROXY-2-QUINOLONES. 175.* REACTION OF 1-ALLYL-3-[(ARYLAMINO)METHYLENE]QUINOLINE-2,4-(1H,3H)-DIONES WITH BROMINE

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

NMR spectroscopy showed that treatment of 1-allyl-3-[(arylamino)methylene]quinoline-2,4-(1H,3H)-diones with an equivalent amount of dry bromine in anhydrous acetic acid leads to the formation of 4-aryliminomethyl-2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinolinium bromides.

Keywords: 1-allyl-3-arylaminomethylenequinoline-2,4-(1H,3H)-diones, enamines, oxazolo[3,2-*a*]-quinolines, Schiff bases, bromination, halocyclization.

By analogy with bromination of other 1-allyl-2-quinolones, the addition of molecular bromine to the corresponding 3-arylaminomethylenequinoline-2,4(1H,3H)-diones in glacial acetic acid proceeds initially as a halocyclization reaction. However, subsequent dilution of the reaction solution by adding water, usually employed for separating the resultant oxazolo[3,2-*a*]quinolines, is accompanied in this case by a further chemical transformation, namely, facile hydrolysis of the enamine fragment. As a result, the major final product is 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carbaldehyde [2].

The question of the structure of the compound undergoing hydrolysis still remains open. In attempting to resolve this question, we repeated the same experiment but under conditions designed to exclude hydrolysis. For this purpose, 1-allyl-3-[(4-bromophenylamino)methylene]quinoline-2,4-(1H,3H)-dione (**1**), which exists predominantly as the (*E*)-isomer [2, 3], was treated with dry bromine in anhydrous acetic acid. Then, the solvent was removed completely under reduced pressure.

Analysis of the ^{1}H NMR spectrum of this product in DMSO-d_6 solution showed that the reaction indeed results only in bromocyclization. This conclusion is based on the finding signals in the aromatic region of the spectrum corresponding to the quinolone and *p*-substituted aniline systems and also a typical set of signals of the aliphatic protons of the 2-bromomethyloxazolidine fragment. Useful information on the structure of this oxazoloquinoline is derived from the nature of the downfield signals: The singlet for the azomethine proton at 9.16 ppm and broad singlet for the OH (or NH) group proton at 14.0 ppm. At the least, the azomethine proton signal at 9.16 ppm unequivocally indicates conversion from the initial enamine structure (in such a case, the

* For Communication 174, see [1].

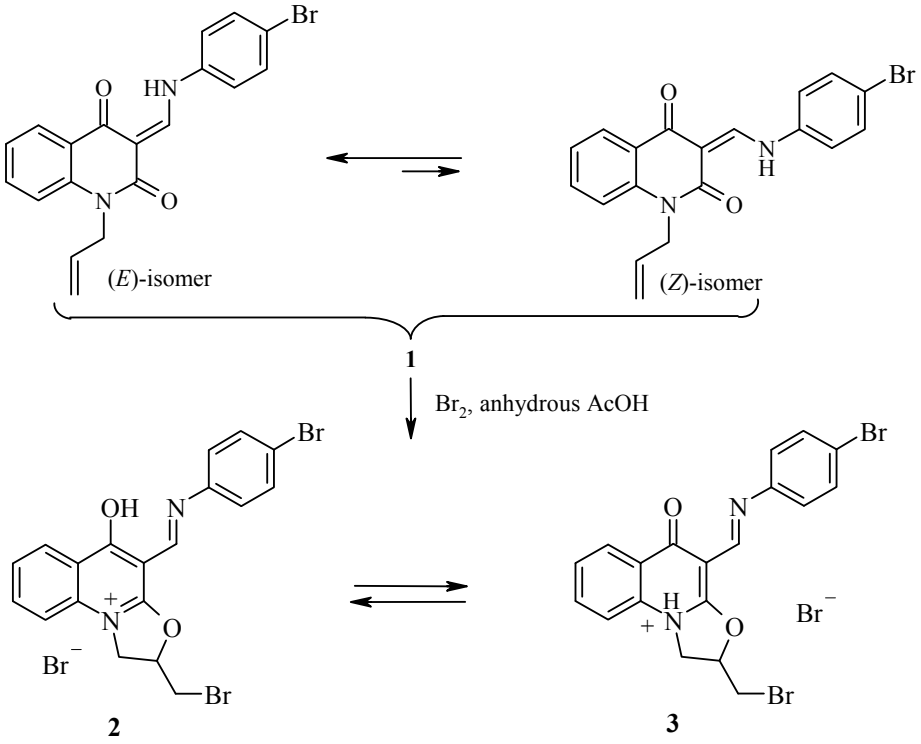
** To whom correspondence should be addressed, e-mail: uiv@kharkov.ua.

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

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 569-574, April, 2010. Original article submitted May 13, 2009.

 0009-3122/10/4604-0452

signal would have appeared as a doublet) to an azomethine structure, i.e., to an ordinary Schiff base. We should note the complete absence of double signals in the spectrum, which indicated that, in contrast to the starting enamine **1**, the product of its bromination is no longer a mixture of geometric (*Z*)- and (*E*)-isomers.



On the whole, the ^{1}H NMR spectrum gives us a general notion of the structure of the compound studied. However, several important details are still unclear. In particular, the quinoline part of the molecule may be represented with equal probability in the aromatic or dihydro form. The available data do not eliminate either possibility. The configuration of the azomethine fragment also remains uncertain. In other words, the ^{1}H NMR spectrum unequivocally indicates only that the product of the reaction of enamine **1** with bromine under anhydrous conditions is the 2-bromomethyl-4-(4-bromophenylimino)methyl derivative of oxazolo[3,2-*a*]quinolinium bromide existing in one of the two possible tautomeric forms (**2** or **3**). Special NMR techniques must be used for a definitive resolution of this structural problem.

Unfortunately, the sample analyzed is not entirely stable in DMSO-d_6 solution. Water present in this solvent causes its partial hydrolysis to 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carbaldehyde and 4-bromoaniline such that a detailed analysis of the NMR spectra is virtually impossible. A sufficiently stable solution is obtained in CF_3CO_2D. Thus, all the subsequent studies were carried out specifically in this solvent although the labile OH (or NH) group protons are, of course, not seen due to rapid deuterium exchange.

We first carried out a precise assignment of the signals in the ^{1}H NMR spectrum. The use of spin-spin coupling was very convenient for this purpose. This is well seen in the COSY spectrum, from which we readily determine that the doublet in the aromatic proton region at 8.43 ppm is linked to the triplet at 7.79 ppm. In turn, this triplet is linked to the triplet at 8.06 ppm, while this latter triplet is linked to the doublet at 7.62 ppm. However, it proved impossible to assign the signals of the aromatic protons of the quinolone fragment on the basis of only these data. For example, each of the doublets at 8.43 and 7.62 ppm may correspond either to H-6

or H-9. The NOESY spectrum, in which correlations are clearly seen between the signals of the N-methylene group of the oxazolidine ring at 5.02 and 4.79 ppm and the doublet at 7.62 ppm, may help to clarify this problem. Hence, it follows that the signal at 7.62 ppm corresponds to H-9, while the downfield doublet at 8.43 ppm corresponds to H-6. The assignment of the other signals does not present any special difficulties and follows from their multiplicities and chemical shifts.

As noted above, it proved impossible to confirm the structure of the product synthesized solely on the basis of the ^{1}H NMR spectrum. It is better to base conclusions on a combined study of the spectra, including the ^{13}C NMR spectra. The number of signals in the ^{13}C NMR spectrum corresponds precisely to the number of atoms in the molecules shown in structures **2** and **3**. Their bonding to different numbers of protons is readily determined using the DEPT-135 spectrum. Thus, we found which signals correspond to the quaternary carbon atoms (these atoms do not have any direct bond with protons and, thus, do not appear in the edited spectrum) and which correspond to the CH or CH_2 groups (their signals are directed upwards and downwards, respectively).

Subsequent, already concrete assignments of the carbon signals were carried out using the two-dimensional ^{1}H-^{13}C heteronuclear correlation spectra through one bond (HMQC) and two or three (sometimes, four) chemical bonds (HMBC). The cross-peak coordinates found are given in Table 1. The correlations found permit the assignment of all the signals in the ^{13}C NMR spectrum of the compound analyzed and drawing conclusions about the structure of this compound. The signals of the protonated carbon atoms may be assigned on the basis of finding correlations through one bond in the HMQC spectrum, while the signals of the quaternary carbon atoms may be assigned on the basis of the set of correlations in the HMBC spectrum. The assignments are given in the scheme below. The most important HMBC correlations used for this purpose are shown by arrows.

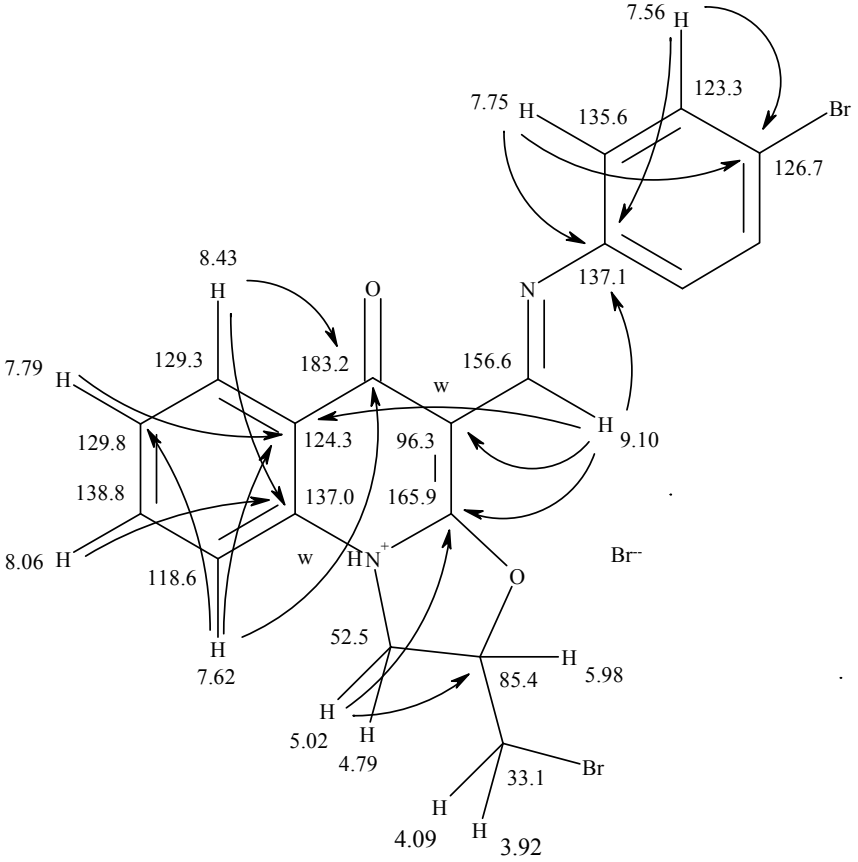


TABLE 1. Complete Listing of ^{1}H-^{13}C Heteronuclear Correlations Found for Oxazoloquinoline Bromide **3**

^{1}H NMR signal, δ, ppm	Position of ^{13}C cross-peaks	
	HMQC	HMBC
9.10	156.6	183.2; 165.9; 137.1; 124.3; 96.3
8.43	129.3	183.2; 138.8; 137.0; 118.6*
8.06	138.8	137.0; 129.3; 124.3*; 118.6
7.79	129.8	124.3; 118.6
7.75	135.6	137.1; 126.7
7.62	118.6	183.2; 129.8; 124.3
7.56	123.3	137.1; 135.6; 126.7
5.98	85.4	165.9; 33.1
5.02	52.5	165.9; 85.4; 33.1
4.79	52.5	165.9; 85.4; 33.1
4.09	33.1	85.4; 52.5
3.92	33.1	85.4; 52.5

* Value of low-intensity correlation.

The chemical shifts of the carbon atoms in the pyridin-4-one ring hold the greatest importance for establishing the structure. Here, the absorption band of C-5 appears at 183.2 ppm, while the corresponding band of C-4 appears at 96.3 ppm. The chemical shift data indicate the absence of conjugation of the double bonds localized in this ring with the benzene ring of the heterocyclic fragment. This would be possible only if the molecule had oxoquinoline structure given by formula **3**. The difference in the chemical shifts of C-4 and C-5 in the 5-hydroxy tautomer **2** should be significantly smaller.

In conclusion, we note that, in the scheme, the azomethine fragment in oxazoloquinolinium bromide **3** is depicted as a (*Z*)-conformer relative to the exocyclic bond between this fragment and the heterocyclic system. Such a structure follows from the finding of a correlation in the HMBC spectrum between the singlet of the CH=N group proton and the signal of C-5a, which is removed by four chemical bonds from this proton. This correlation is attributed to a *w*-interaction, which obtains only with a zigzag arrangement of the bonds found between the interacting magnetic nuclei.

EXPERIMENTAL

The ^{1}H and ^{13}C spectra of oxazoloquninoline bromide **3**, the two-dimensional ^{1}H NMR COSY experiments and the NOESY-2D and DEPT-135 homonuclear Overhauser effect experiments, as well as the heteronuclear HMQC and HMBC correlation spectra were taken on a Varian Mercury-400 spectrometer at 400 and 100 MHZ, respectively. All the two-dimensional experiments were carried out with gradient selection of the useful signals. The mixing time in the pulse sequences was $^{1}J_{CH} = 140$ and $^{2\text{-}3}J_{CH} = 8$ Hz. The number of increments in the COSY and HMQC spectra was 128, while this number in the HMBC was 400. The mixing time in the NOESY-2D experiment was 500 msec with DMSO-d_6 or CF_3CO2D as the solvent and TMS as the internal standard. A sample of starting 1-allyl-3-[(bromophenylamino)methylene]quinoline-2,4(1H,3H)-dione (**1**) was obtained according to our previous procedure [2]. Water was removed from commercial acetic acid by drying over P_2O_5, while water was removed from bromine by shaking with concentrated sulfuric acid.

2-Bromomethyl-4-[(bromophenylimino)methyl]-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinolinium Bromide (3). A solution of dry bromine (0.52 ml, 0.01 mol) in anhydrous acetic acid (5 ml) was added to a solution of 1-allyl-3-[(4-bromophenylamino)methylene]quinoline-2,4(1H,3H)-dione (**1**) (3.83 g, 0.01 mol) in

50 ml anhydrous acetic acid. The red-brown color of the bromine disappeared almost immediately. The solvent was completely removed from the reaction mixture at reduced pressure to give a quantitative yield 5.40 g oxazoloquinolinium bromide **3**, which is a light-yellow crystalline compound with mp 241-243°C. ^{1}H NMR spectrum in CF_3CO_2D, δ, ppm (*J*, Hz): 9.10 (1H, s, CH=N); 8.43 (1H, d, *J*= 8.0, H-6); 8.06 (1H, t, *J* = 7.6, H-8); 7.79 (1H, t, *J* = 7.2, H-7), 7.75 (2H, d, *J* = 8.4, H-2', H-6'), 7.62 (1H, d, *J* = 10.8, H-9), 7.56 (2H, d, *J* = 8.4, H-3', H-5'); 5.98 (1H, m, $NCH_2C\underline{H}O$); 5.02 (1H, t, *J* = 9.9, NCH); 4.79 (1H, dd, *J* = 10.0 and *J* = 5.6, NCH); 4.09 (1H, d, *J*= 12.4, CHBr); 3.92 (1H, d, *J* = 11.6, CHBr). ^{13}C NMR spectrum (in CF_3CO_2D), δ, ppm: 183.2 (5-C=O), 165.9 (C-3a), 156.6 (4-C=N), 138.8 (C-8), 137.1 (C-1'), 137.0 (C-9a), 135.6 (C-2', C-6'), 129.8 (C-7), 129.3 (C-6), 126.7 (C-4'), 124.3 (C-5a), 123.3 (C-3', C-5'), 118.6 (C-9), 96.3 (C-4), 85.4 ($NCH_2\underline{C}HO$), 52.5 (NCH_2), 33.1 (CH_2Br). Found, %: C 41.94; H 2.67; N 5.03. $C_{19}H_{15}Br_2N_2O_2 \cdot Br$. Calculated, %: C 42.02; H 2.78; N 5.16.

REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, A. A. Davidenko, and A. K. Yarosh, *Khim. Geterotsikl. Soedin.*, 560 (2010). [*Chem. Heterocycl. Comp.*, **46**, 445 (2010)].
2. I. V. Ukrainets, Liu Yangyang, N. L. Bereznyakova, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 1539 (2009). [*Chem. Heterocycl. Comp.*, **45**, 1235 (2009)].
3. I. V. Ukrainets, Liu Yanyang, A. A. Tkach, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 1015 (2009). [*Chem. Heterocycl. Comp.*, **45**, 802 (2009)].