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Reaction of 3-chloroquinoline-2,4-diones with ethanolamine and rearrangement of the reaction products

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ABSTRACT

The reaction of tertiary α -chloroketones with ethanolamine has not been hitherto described in the literature. Herein, we describe the reaction of tertiary 3-chloroquinoline-2,4-diones with ethanolamine to give novel 3-(2-hydroxyethylamino)quinoline-2,4-diones. These compounds provide 3-(2-oxooxazolidin-3-yl)quinoline-2,4(1*H*,3*H*)-diones and new compounds with dimeric character after reaction with triphosgene. Molecular rearrangement proceeds during the reaction of 3-(2-hydroxyethylamino)quinoline-2,4-diones with isocyanic acid. Three types of reaction products arise: 2-(2-hydroxyethyl)imidazo[1,5-*c*]quinazoline-3,5-diones, 3-(2-hydroxyethyl)-3,3a-dihydro-2*H*-imidazo[4,5-]quinoline-4(5*H*)-diones and primarily 5-hydroxy-1-(hydroxyethyl)-1'*H*-spiro[imidazolidine-5,3'-indole]-2,2'-diones. The reaction mechanism and product stereochemistry are discussed. The ¹H, ¹³C and ¹⁵N NMR spectra of the prepared compounds were measured, and all resonances were assigned from appropriate two-dimensional experiments.

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1. Introduction

In our previous paper we studied the reaction of 3-chloroquinoline-2,4-diones **2** with ammonia and primary amines.¹ The reaction proceeded smoothly and 3-amino or 3-alkylaminoquinoline-2,4-diones were prepared in good yields. These compounds rearrange during reaction with urea,^{2,3} nitro-urea,^{4,5} isocyanates,⁶ isothiocyanates,^{7–9} and isocyanic and isothiocyanic acids^{10,11} to give a broad palette of new heterocyclic compounds: imidazo[1,5-*c*]quinazoline-3,5-diones, 3-(3-acylureido)-2,3-dihydro-1*H*-indol-2-ones, 4-alkylidene-1'*H*-spiro[imidazolidine-5,3'-indole]-2,2'-diones and spiro-linked imidazoline-2-thiones. 3-Aminoquinoline-2,4-quinolinediones were also reduced¹² by NaBH₄ and the reaction products were converted to 3-alkyl/aryl-2,3-dihydro-1*H*-indol-2-ones. With regard to the interesting results described above, we carried out some of the aforementioned reactions using an amine containing yet another functional group, potentially capable to participate during the molecular rearrangement.

In this paper, we describe the reactions of 3-chloroquinoline-

2,4-diones **2** with easily accessible and inexpensive ethanolamine. We presumed that the reaction would proceed through the formation of 3-(3-hydroxyethyl)amino derivatives **3**, whose reactions with isocyanic acid can lead, according to our experiences, to more complex products of the molecular rearrangements than as with simple 3-alkylaminoquinolinediones.

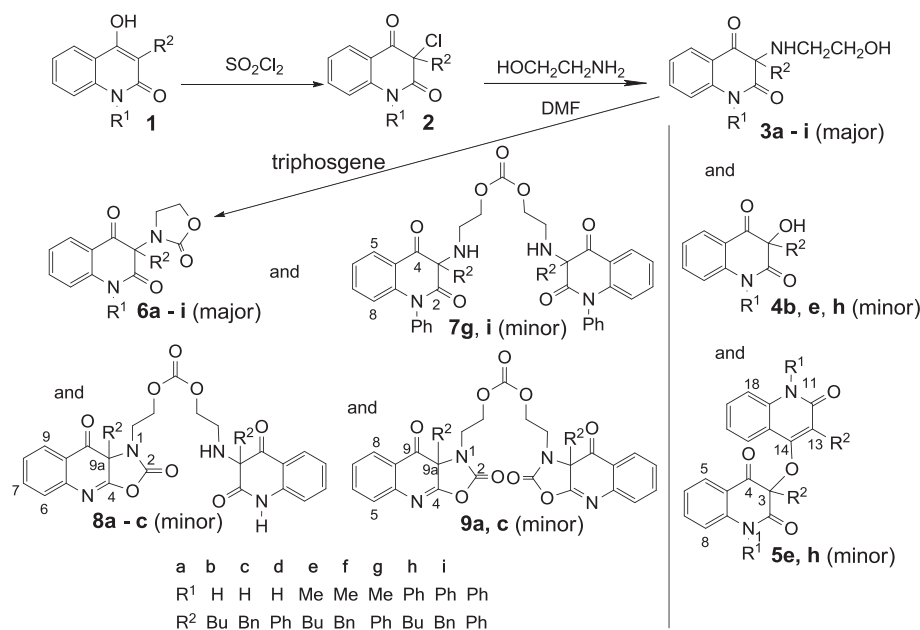
2. Results and discussion

The reaction of **2** with ethanolamine (Scheme 1) proceeded easily and in good yields (Table 1). In all cases, 3-(3-hydroxyethyl)amino derivatives **3** were obtained, and their NMR spectra are given in Table 2. When substituent R² was a benzyl group, 3-hydroxyderivatives **4b**, **e**, **h** and minor compounds **5e**, **h** were also obtained.

The formation of compounds **4** was the result of the hydrolysis of **3**. The structure of the condensation products **5** was established by the analysis of very complicated NMR spectra (Table 3), in which the chemical shifts of –OH groups were absent. These compounds arose from the reaction of 3-chloroderivatives **2** with 4-hydroxyquinolin-2-one **1**, stemming from the reductive hydrolysis of **2** in alkaline medium. The conversion of **2** to **1** in alkaline medium is known.¹³ The structures of **5e** and **5h** were confirmed by their synthesis from **1** and **2**, though in very small yields. The main

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Scheme 1.

Table 1
Reaction of 3-chloroquinolinediones **2** with ethanolamine.

| Starting compound | Product(s), (yield, %) |
|-------------------|---|
| 2a | 3a (51) |
| 2b | 3b (24), 2b (3), 4b (11) |
| 2c | 3c (69) |
| 2d | 3d (68) |
| 2e | 3e (31), 4e (15), 5e (4) |
| 2f | 3f (88) |
| 2g | 3g (65) |
| 2h | 3h (17), 4h (9), 5h (5) |
| 2i | 3i (56) |

product was starting compound **1**, arising from the reductive hydrolysis of **2**.

After obtaining compounds **3**, we studied their reaction with triphosgene in order to install an additional ring on the molecule. We obtained compounds **6** in all cases (Table 4), and their NMR spectra are given in Table 5. The structure of compounds **6** were also proposed according to the results obtained from ESI-MS experiments. In the first-order mass spectra of compounds **6** the sodium adduct of the molecule $[M+Na]^+$ represents the most abundant ion (except for compound **6a**). This signal was usually accompanied by a singly charged signal that was twice as high, which we assigned to the sodium adduct of the dimer $[2 \cdot M + Na]^+$. Furthermore, we studied the gas-phase behavior of compounds **6** in detail using ESI-MS/MS experiments under collision-induced dissociation (CID). In the ESI-MS/MS spectra of compounds **6a**, **6d** and **6g**, three independent neutral losses were observed. These neutral losses were assigned as a water molecule (18 m/z), carbon dioxide (44 m/z) and C_4H_8 from the butyl chain (56 m/z). Only one neutral loss at m/z 87 was observed in the case of compounds **6b**, **6e** and **6h**. According to the structures of these compounds, we propose that the covalent bond between C(3) and the nitrogen atom was cleaved and the neutral loss of oxazolidin-2-one (87 m/z) occurred. In the case of compounds **6b**, **6e** and **6h**, the $[M+H]^+$ ion was not successfully isolated, and tandem mass spectra were not recorded.

In several cases, minor compounds were also obtained from the

reaction of **3** with triphosgene, identified as dimeric compounds **7**, **8**, and **9** (Scheme 1, Tables 6 and 7). Compounds **7** were symmetric dimers created from two molecules of compound **3** and triphosgene and signals corresponding to one carbon possessed half the intensity of the other signals in their ^{13}C NMR spectra. Moreover, these signals showed the appropriate cross-peaks in the 2D $^1H-^{13}C$ HMBSC spectrum due to existence of $^3J(^{13}C, OCH_2)$, providing clear evidence for the existence of an $OC(=O)O$ fragment in compounds **7**. Proton signals from NH groups were not detected probably due to rapid exchange with water protons, but their presence follows from MS data.

The precursors of compounds **9** contained NH protons in position 1; however, no acidic protons were detected in the 1H NMR spectra of **9** (Table 6). Two types of $C=O$ groups in a ratio of 2:1 were found in the NMR spectra of compounds **9**. The correlation between the protons in the OCH_2 group and the carbonyl group of relative intensity one and correlation of protons of NCH_2 group and the carbonyl group with a two-fold intensity through $^3J(C=O, CH_2)$ in HMBSC spectra help correct the structure of **9**. The 2D $^1H-^{15}N$ in the HMBSC spectra of compounds **9** were of key importance in the correct determination of their constitution because the ^{15}N chemical shifts resonating at ca. -145 ppm clearly indicate the presence of a so-called "pyridine" type of nitrogen in the molecule. The alternative possibility corresponding to the existence of a $N-C(=O)-N$ fragment instead of $O-C(=O)-N$ can thus be excluded. Compounds **8** are unsymmetric and likely arise from the reaction of **7** with an additional molecule of triphosgene. The 1H and ^{13}C NMR spectra of compounds **8** (Table 7) are rather complicated, but the typical chemical shifts observed in symmetrical compounds **7** and **9** were relatively easily detected in these spectra. Thus, compounds **8** contain - in one molecule - structural motifs from both compounds **7** and **9**. Analogously, the ^{15}N chemical shifts resonating at ca. -144 ppm and (-285 ± 5) ppm belong to a structural motif that is similar to that from compound **7**, and those observed at ca. -241 ppm and (-341 ± 3) ppm belong to a structural motif that is similar to that from compound **9**.

The formation of compounds **7**, **8**, and **9** is rather surprising and shows that, in the presence of catalytic *N,N*-dimethylaminopyridine, triphosgene can react with not only the amino group, but also

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