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4-HYDROXY-2-QUINOLONES. 167*. STUDY OF THE REACTION OF ETHYL 1-ALKYL-SUBSTITUTED 4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLATES WITH PHOSPHORUS OXYCHLORIDE

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Prolonged treatment of ethyl 1-alkyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates with refluxing phosphorus oxychloride gives not only the target 4-chloro derivatives but is also accompanied by a marked loss of the 1-N-alkyl groups to form the side product 2,4-dichloro-3-ethoxycarbonylquinoline.

Keywords: ethyl 1-alkyl-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylates, phosphorus oxychloride, desalkylation.

Thanks to their high reactivity 3-substituted 4-chloro-2-oxo-1,2-dihydroquinolines readily react with many nucleophiles and are of interest for the synthesis of very different products. The most convenient method for their preparation is treatment of the corresponding 4-hydroxy derivatives with phosphorus oxychloride or its mixture with phosphorus pentachloride [2, 3]. As a rule, such reactions are readily carried out and proceed to give results as anticipated although sometimes a marked increase in the yields and purities of the final 4-chloro-2-quinolones is only achieved through the addition of basic catalysts to markedly ease the exchange of the 4-hydroxy group for halogen [4]. Up to this time it has not been considered that the 1-N-alkyl substituents are affected by this and their removal is only possible under much more forcing conditions, e.g. by fusion with phosphorus pentachloride [2]. For this reason it is likely that a detailed study of the features of the reaction of 1-substituted 4-hydroxy-2-quinolones to their 4-chloro derivatives using phosphorus oxychloride has not received the required attention and in the scientific literature one meets a very wide variation in reaction time (from 1 to 16 h) [4-8]. However, in none of these does one find data explaining why a particular reaction times was used. At the same time, experiments carried out by us have shown that, at least in the case of 1-alkyl-substituted 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines, this factor has an extremely significant effect on the purity of the 4-chloro substituted derivatives obtained.

* For Communication 166 see [1].

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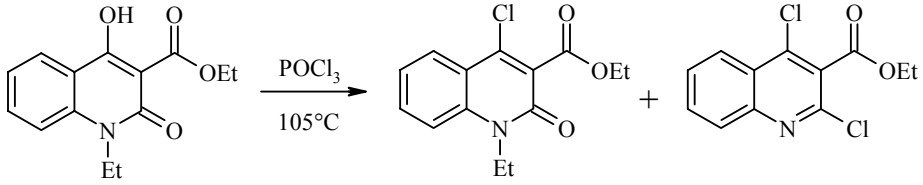
The behavior noted in the reaction between phosphorus oxychloride and ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate with long N-alkyl substituents (beginning with butyl) serves as the basis for carrying out this type of study. Thus, if after conventionally refluxing the reaction mixture for 1-2 h, the separation of the target reaction product is not carried out immediately but for some reason left to the following day then serious complications can occur namely the formed 4-chloro derivative proves to be very difficult to convert to the crystalline state. Such problems do not arise with an ordinary synthesis hence it is quite apparent that prolonged contact of 1-alkyl-substituted 4-hydroxyquinol-2-ones with phosphorus oxychloride is accompanied not only by exchange of the 4-hydroxy group for chlorine but also by other more profound chemical processes.

To resolve this question, chromatographically pure ethyl 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) was refluxed with phosphorus oxychloride with regular removal of a sample which then underwent chromato mass-spectrometric analysis.



1 **2** **3**

It was firstly and unexpectedly revealed that exchange of the 4-hydroxy group for chlorine occurs very rapidly. Even after 5 min the starting ester **1** was not found in the reaction mixture and the single reaction product was ethyl 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**2**). Continuing the experiment gave no less interesting results. Hence, judged by the chromato-mass spectrometric monitoring data, at approximately 45 min after the start there appeared a new substance in the reaction mixture and this was identified initially by mass and then by ^{1}H NMR spectroscopy as ethyl 2,4-dichloroquinoline-3-carboxylate (**3**). Over the course of time the content of this product gradually increased and at 10 h it already exceeded 25% (Table 1). Hence we have experimentally confirmed that refluxing N-alkyl-substituted 4-hydroxyquinol-2-ones in phosphorus oxychloride (up to this time considered *a priori* as a single process for preparing the corresponding 1-alkyl-4-chloroquinol-2-ones) is actually accompanied by an unwanted removal of N-alkyl groups.

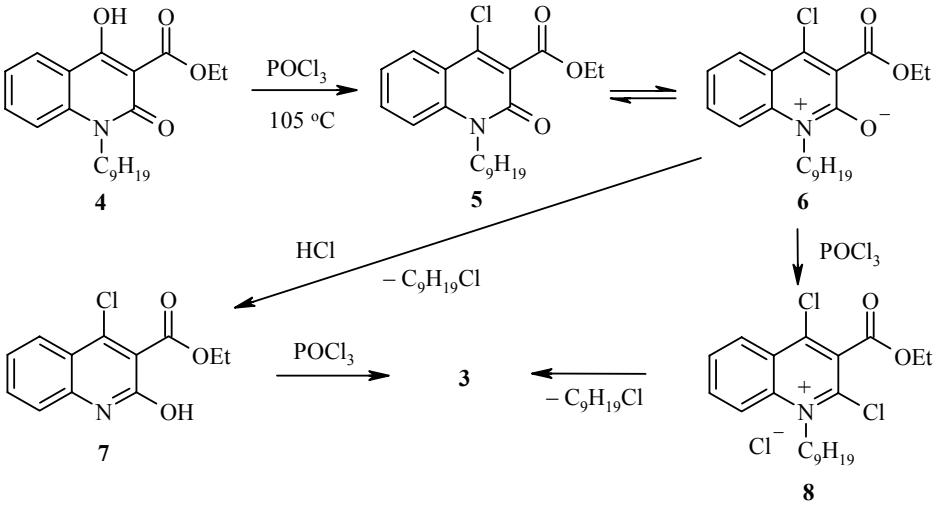
TABLE 1. Reaction Products of Ethyl 1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) with $POCl_3$ (Chromato Mass-Spectrometric Analysis)

Reaction time, min	Content of the compounds in the reaction mixture, %	
	4-Cl-ester **2**	2,4-Cl_2-ester **3**
5	100	0
15	100	0
30	100	0
45	99.8	0.2
60	99.5	0.5
75	99.3	0.7
90	99.2	0.8
105	99.1	0.9
120	98.9	1.1
180	94.1	5.9
600	74.7	25.3

To obtain more detailed information allowing an assessment of the mechanism occurring in these processes the reaction with phosphorus oxychloride was additionally undertaken with ethyl 4-hydroxy-1-nonyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**4**). The choice of this compound as the subject of the study was firstly based on the high molecular weight of the N-alkyl substituent. Thanks to this factor the likelihood of finding some kind of nonquinoline nonyl derivative and subsequently deriving its structure was significantly increased.

The first stage of the studied reaction in this case is undoubtedly the exchange of the 4-OH group for chlorine. After refluxing for 120 h in phosphorus oxychloride the 4-chloro derivatives **5** is fully converted to the 2,4-dichloroquinoline **3** thus losing the N-nonyl substituent, proving to be in the form of nonyl chloride. It then became clear that, arising sometimes and giving complexity to our study of the separation and purification of ethyl 1-alkyl-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylates is just due to higher alkyl chloride by products.

We have previously shown that, in the case of 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydro-quinolines unsubstituted at position 1 there is a primary and very ready exchange of the 2-OH group for chlorine [9]. This suggests that such compounds are converted to the 2,4-dihydroxy form when dissolved in phosphorus oxychloride. The ability to form the structurally similar aromatic bipolar resonance forms of type **6** has also been noted in N-alkyl-substituted quinol-2-ones [10]. In fact, such forms are salts of quaternary ammonium bases. Hence, it is not surprising that the presence of clear chloride nucleophiles in the reaction medium implies an ordinary substitution of the quaternary nitrogen for halogen to form an alkyl chloride in the final step [11, 12], which is confirmed experimentally.



Loss of the N-alkyl group can occur only from the quaternized heterocyclic base, e.g. from the bipolar form **6**. However, its contribution to the resonance hybrid of ester **5** is small so the observed rate of conversion of the 1-alkyl-substituted 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines to the 2,4-dichloroquinoline **3** is comparatively low. Thus the limiting stage of all of the reactions is most of all, in fact, desalkylation since after formation of the 2-hydroxyquinoline **7** the obstacles to rapid formation of the dichloro derivative **3** no longer remain. An alternative mechanism involving initial formation of 1-nonyl-2,4-dichloroquinolinium chloride **8** is less likely. In the first place, if realized the presence in the reaction mixture of N-alkyl-substituted 4-chloro-2-oxo-1,2-dihydroquinolines would scarcely be possible over a prolonged intermediate time and is contradicted by the experimental data (see Table 1). In the second, at least with the chromato-mass spectrometric monitoring of the course of the reaction of esters **1** or **4** with phosphorus oxychloride there were not detected even traces

of the corresponding dichloro-substituted quinolines with 1-N-alkyl substituents. However, the arguments given are certainly not strictly conclusive since it is well known that the predominant route for the thermal cleavage of quaternary ammonium base halides when recorded by mass spectrometry is removal of an N-alkyl group as an alkyl halide [13]. In other words, the experimental chromato-mass spectra of the 2,4-dichloroquinoline **3** and the nonyl chloride observed might equally be considered as the result of a "normal" thermal degradation of the dichloroquinolinium chloride **8** (under conditions where it is actually formed).

Hence it is possible to make an unambiguous deduction from the experiments we carried out. In the preparation of 1-alkyl-substituted 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylates the contact of the starting 4-hydroxy derivatives with phosphorus oxychloride should not exceed 30 min in order to avoid side reactions. Moreover, it should be kept in mind that the rate of desalkylation of amines depends on the structure of the alkyl fragment [12] to a marked degree. In the case of readily eliminated 1-N-alkyl or, for example, benzyl substituents the length of the reaction should likely be still shorter.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were measured on a Varian Mercury VX-200 instrument (200 MHz) using DMSO-d_6 with TMS as internal standard. Chromato-mass spectrometric investigation was carried out on a Varian 1200L instrument in full scanning mode in the range 35-700 *m/z* with electron impact ionization energy 70 eV, CP-SIL 8CB chromatographic column of length 50 m and internal diameter 0.25 mm, polysiloxane stationary phase (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm, helium gas carrier, injector temperature 300ºC, and ion source temperature 250ºC. Samples of esters **2** and **3** prepared by a known method [14] were used as standards in the mass spectrometric investigation.

Study of the Reaction of Ethyl 1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (1) with $POCl_3$. A solution of chromatographically pure compound **1** (5.22 g, 0.02 mol) in freshly distilled $POCl_3$ (25 ml) was refluxed and samples (0.5 ml) were regularly removed (see Table 1 for intervals) for chromato-mass spectrometric analysis. All samples were initially poured into a mixture of ground ice and water. After decomposition of $POCl_3$ samples intended for determination of the 4-OH ester **1** content were partially neutralized with Na_2CO_3 to pH ~ 4. For determination of the side 2,4-dihcloro-substituted ester **3** Na_2CO_3 was added to pH ~ 8. Reaction products were extracted from each sample using CH_2Cl_2 (5 ml) and the obtained solutions were then used in the chromato-mass spectrometric study.

Study of the Reaction of Ethyl 4-Hydroxy-1-nonyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (4) with $POCl_3$. A solution of compound **4** (10.77 g, 0.03 mol) in freshly distilled $POCl_3$ (50 ml) was refluxed for 120 h. The cooled reaction mixture was poured onto ice and, after decomposition of the $POCl_3$, Na_2CO_3 was added to pH ~ 8, extracted with hexane (3×30 ml), and the extract was evaporated half the initial volume. A sample (0.5 ml) of the solution obtained underwent chromato mass spectrometric analysis and the residue was placed in a freezer at -20ºC for 1 day. The precipitated 2,4-dichloro-substituted ester **3** was filtered, washed with cold hexane, and dried to give the product (6.32 g, 78%). Additional recrystallization from hexane gave colorless crystals with mp 85-87ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.25 (1H, dd, J = 8.2 and J = 1.3, H-5); 8.07 (1H, dd, J = 8.4 and J = 1.7, H-8); 8.00 (1H, td, J = 7.6 and J = 1.5, H-7); 7.86 (1H, td, J = 7.6 and J = 1.5, H-6); 4.48 (2H, q, J = 7.0, OCH_2); 1.36 (3H, t, J = 7.1, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 269 $[M]^+$ (24), 241 $[M-CO]^+$ (27), 224 $[M-OEt]^+$ (100), 196 (23), 161 (46), 135 (13), 99 (27). Values for *m/z* are only quoted for the ^{35}Cl isotope. A mixed sample with a known sample of ester **3** [14] did not give a depression of melting point and the chromato mass and ^{1}H NMR spectra were identical for these materials.

The solvent from the filtrate obtained after separation of the 2,4-dichloro-substituted ester **3** was evaporated. The residue was then distilled using a reflux condenser (20 cm) collecting the fraction with bp 202-204ºC to give pure nonyl chloride (1.62 ml, 29%). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.60 (2H, t, *J* = 6.6, $ClCH_2$); 1.68 (2H, q, *J* = 7.1, $ClCH_2C\underline{H}_2$); 1.40-1.17 (12H, m, $(C\underline{H}_2)_6$–CH_3); 0.84 (3H, t, *J* = 6.7, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 119 $[M\text{-}C_3H_7]^+$ (1), 105 $[M\text{-}C_4H_9]^+$ (49), 97 (26), 91 $[M\text{-}C_5H_{11}]^+$ (100), 83 (48), 71 (47). The experimental mass spectrum was identical to that of a standard sample of nonyl chloride taken from the internal library of the mass spectrometer.

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