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New heterocyclic analogues of rhodamines

M.P. Shandura, Ye.M. Poronik, Yu.P. Kovtun*

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Str. 5, 02094 Kyiv, Ukraine

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Abstract

Double formylation of 9-methylpyronine yielded the corresponding 9-diformylmethinexanthene which was heterocyclized to furnish 9-hetarylpyronines. The chemical and spectral behaviour of the rhodamine analogues thus obtained was studied.

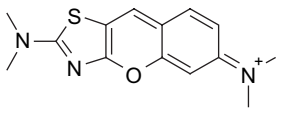
Keywords: Pyronine; Rhodamine; Visible spectra; Fluorescence spectra; Fluorescence quantum yield

1. Introduction

The measurement of fluorescence has become a very useful tool in medical and biological diagnostics as well as in environmental analysis and material sciences due to high sensitivity of fluorescence spectroscopy. Many techniques and analytical concepts use fluorescent dyes, in particular rhodamines, for the labeling of biological compounds, e.g. antibodies or DNA [1]. Rhodamines are particularly useful as laser dyes [2].

The above-mentioned applications as well as other practical uses call for the possibility of modifying an initial luminophore structure so as to adjust its spectral and chemical properties for a specific requirement. Although rhodamines are widely used as luminophores for almost all of the last century, nevertheless synthetic approaches to these compounds remain unchanged: they are mostly prepared by condensation of aromatic aldehydes with *m*-aminophenols followed by oxidation of the intermediate product.

There are very few other synthetic routes to rhodamine-like structures, with two noteworthy methods based on the substitution of the benzene ring by a thiazole ring (yielding A type compounds) [3] and the exchange of the oxygen bridge for a methylene bridge (yielding B type compounds, carbopyronines) [4].



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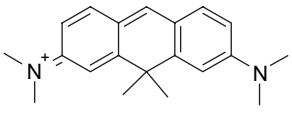

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We have recently shown that the 9-methylpyronine nucleus **1** can be employed in cyanine condensations [5]. In the present work, we involved the highly reactive methyl group of compound **1** in other conversions leading to a number of 9-hetarylpyronines.

2. Results and discussion

During formylating 9-methylpyronine **1** with the Vilsmeier reagent, an intensely fluorescing red dye was formed. The ^{1}H NMR spectra, along with the data of elemental analysis (see Section 3), suggested that the Vilsmeier double formylation occurred to give the iminium salt **2**. Formation of similar derivatives (or free dialdehydes very readily produced by hydrolysis) was previously reported for other compounds containing an active methyl group (such as quaternary salts of quinoline, benzothiazole, etc.) [6]. However, the reaction of compound **1** is remarkable for its selectivity (no monoformylated product

* Corresponding author. Tel.: +380 44 5510682; fax: +380 44 5732643.
E-mail address: yu_kovtun@svitonline.com (Yu.P. Kovtun).

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was detected), high rate, and a good product yield. Bis-quaternary ammonium salt **2** is stable to water and acids. When treated with alkali under mild conditions, it is partially hydrolyzed to provide the dimethylaminoacrolein derivative **3** whereas short boiling in aqueous alcoholic alkali furnishes dialdehyde **4** in high yield (see Scheme 1).

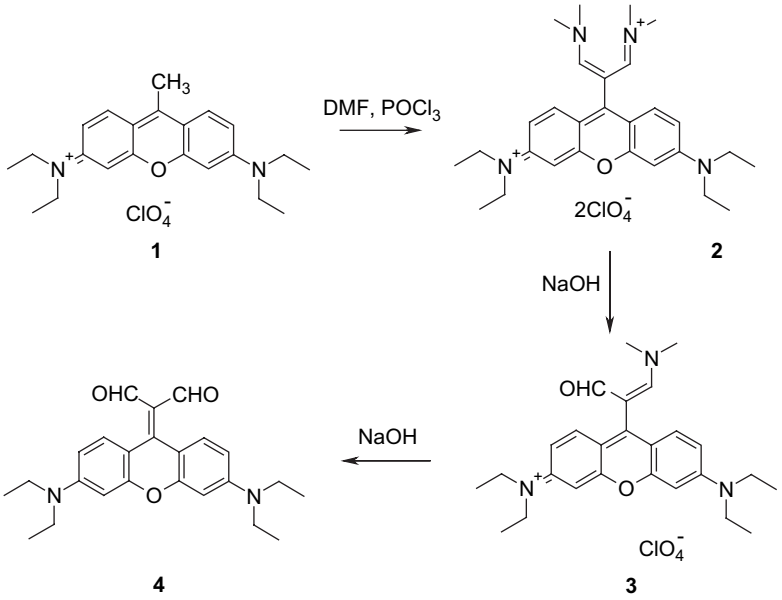
The hetarylidene malonaldehyde derivative **4** is a rather deeply coloured substance exhibiting an intermediate type of solvatochromism (λ_{max} is 515 nm in toluene, 547 nm in ethanol, and 537 nm in acetonitrile or DMF). It can be condensed with various nucleophiles. Using reagents with two nucleophilic centres, one can obtain the corresponding heterocyclic analogues of rhodamine dyes. For instance, condensation of **4** with phenylhydrazines leads to pyrazoles **5** and **6**, and the reaction with hydroxylamine hydrochloride yields isoxazole **7** which undergoes ring opening in a weakly alkaline medium to give cyanoaldehyde **8**. The isoxazole-ring openings are known to proceed under severe conditions but the reaction is facilitated in the case under study due to a strong electron-acceptor substituent at position 4 of the isoxazole ring. The ring opening takes place even on treating isoxazole **7** with an aqueous Na_2CO_3 or K_2CO_3 solutions and also occurs on heating **7** above 100 °C (an absorption band with λ_{max} 464 nm appears in the electronic spectra indicating the aldehyde **8** formation). This bielectrophilic reagent can serve as a substrate in the synthesis of new heterocyclic derivatives. In particular, aminopyrazole **9** was thus obtained (see Scheme 2).

The attempted synthesis of the mercaptopyrimidine derivative by the reaction of dialdehyde **4** with thiourea has demonstrated that the cyclization takes another route under basic catalysis. Only one aldehyde group and the double bond of compound **4** are involved in the reaction to provide spiro compound **10** (see Scheme 3). The absorption spectra maximum of this substance is found at 320 nm (in EtOH), the observed hypsochromic shift arises because of breaking conjugation system in the xanthene chromophore. The ^{1}H NMR spectrum registered in DMSO-d_6 exhibits the singlet signals of the proton at position 4 of the pyrimidine ring at 7.31 ppm and the aldehyde proton at 9.02 ppm as well as two broad singlets caused by the NH protons at 9.66 and 10.4 ppm.

Another example of the high reactivity of the methyl group in compound **1** was the reaction with pyridinium bromide perbromide carried out in pyridine. As an intermediate, the bromomethyl derivative is formed which alkylates pyridine and finally yields **11** (see Scheme 4).

The spectral luminescent characteristics of the compounds synthesized are listed in Table 1. As can be seen from the table, all products absorption maxima are at 15–57 nm longer wavelengths than in the starting pyronine **1**. This effect is induced by the electron-acceptor substituents at position 9 of the dye molecule. The most red-shifted absorption is observed for dicationic dyes **2** and **11**. In the presence of acid dialdehyde **4** switches from the merocyanine to cationic form, the latter also absorbing at longer wavelengths than pyronine **1**. The fluorescence spectra of the obtained substances appear as mirror images of their absorption spectra, with the Stokes shifts of 20–25 nm, which is typical to rhodamines. Fluorescence quantum yields are comparable to that of the starting pyronine **1**.

Though aminopyrazole **9** is almost nonfluorescent, it starts emitting light on adding an equivalent amount of acid. The origin of the effect is that fluorescence quenching in amines requires the free pair of electrons localized on the nitrogen. If this electron pair is bound to proton, then electron transfer is inhibited, and fluorescence is not quenched. Such molecules are said to undergo photoinduced electron transfer (PET), which is light-induced transfer of electron from the nitrogen into the fluorophore system. At low pH, the amino group is protonated and does not quench the pyronine system. As the



Scheme 1.