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TOWARDS UNDERSTANDING THE RICHTER REACTION. PECULIARITIES OF HETEROCYCLIZATION OF 3-DIETHYLAMINO-6-(HEPTYN-1-YL)-1,4-NAPHTHOQUINONE-5-DIAZONIUM CHLORIDE

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Abstract: Heterocyclization of 3-diethylamino-6-heptyn-1-yl-1,4-naphthoquinone-5-diazonium chloride results in the formation of five- or six-membered ring containing products depending on the reaction conditions. A common intermediate was isolated. Possible reaction mechanisms are discussed.

Heterocyclization of *ortho*-alkynylarene diazonium salts *via* diazotization of the corresponding *ortho*-aminoalkynylarenes (the Richter reaction) is a method of preparing condensed pyridazines.[1] We found recently, that the diazotization of 2-alkynyl-1-amino-9,10-anthraquinones is followed by formation of five-membered pyrazoles.[2]

In the present work, the diazotization and heterocyclization of 5-amino-3-diethylamino-6-(heptyn-1-yl)-1,4-naphthoquinone **1** were studied. Compound **1**, which has the same steric environment at the reaction centre as 2-alkynyl-1-amino-9,10-anthraquinones, contains the diethylamino group which decreases substantially the electron-acceptor influence of the quinonoid core. We assumed that if the direction of cyclization is determined by electronic factors, both five- and six-membered ring containing products may be formed from compound **1**.

Therefore, we separated the stages of diazotization and cyclization. We performed the diazotization of **1** using a three-fold excess of $NaNO_2$ in a mixture of 18% aqueous HCl with acetone (1:1) at 20°C. Under these conditions, diazonium salt **2** was formed immediately after mixing the reagents. We then diluted the reaction mixture with a 10-fold amount of either water or 18% aqueous HCl, to allow heterocyclization of the diazonium salt **2**. The progress of the reaction was indicated by changes in the colour of the reaction mixture.

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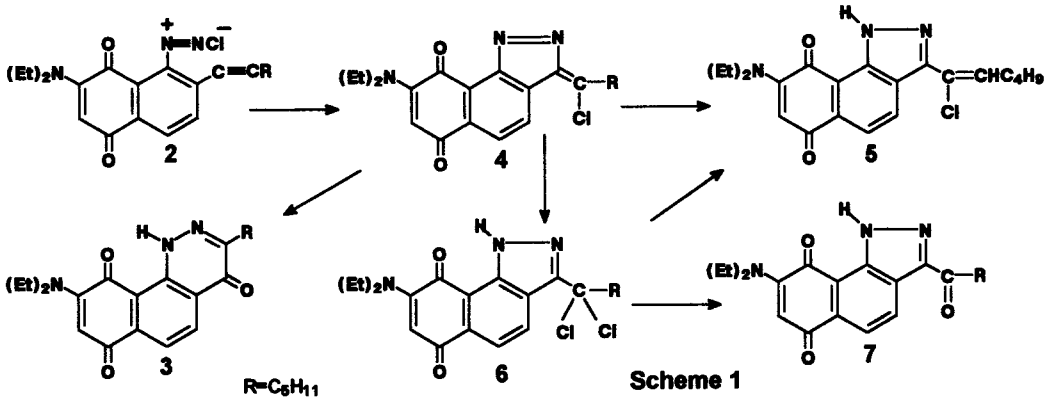
It was found that heterocyclization of **2** gives rise to various reaction products depending on the reaction conditions (Scheme 1). When the reaction solution was diluted by water, the cyclization of **2** took 6 h and gave compound **3** (80%). In strongly acidic aqueous solution, the reaction only took 2 h but the yield of **3** was considerably reduced because of hydrolysis of the diethylamino group. In this case, we found that the cyclization intermediate **4** was formed quickly after dilution of the reaction solution by 18% aqueous HCl. Interruption of the process after 5 min allowed isolation of **4** in a 79% yield. Transfer of this intermediate to an organic solution by shaking the reaction mixture with $CHCl_3$ prevented hydrolysis and increased the reaction time for conversion to **3** up to 7 h. In this case, we isolated a mixture consisting of **3** (~25%), **5** (~16%), and **6** (~60%), the total yield being 90%. The structure of **6** was not unambiguously confirmed because of its high lability. However, from spectral data and previous experience[2] we assumed it to be 3-(1,1-dichlorohexyl)-8-diethylamino-1*H*-benzo[*g*]indazole-6,9-dione as shown. The presence of the pyrazole in **6** was confirmed by the position of the absorption band of the NH stretching vibrations in the IR-spectrum and by the NH proton signal in the ^1H NMR spectrum (Table 1). On chromatography on silica gel in $CHCl_3$, **6** transforms quantitatively into **5** and **7**.



Scheme 1

The structure of the intermediate **4** was determined from analytical and spectral data[3] as well as from its chemical behaviour. In $CHCl_3$, on silica gel, this labile compound was converted into products **3**, **5**, **7**. The conversion of **4** into **5** may be understood as an isomerisation of a compound with an exo-double bond into its more stable endo-isomer *via* a prototropic rearrangement (Scheme 2). According to spectroscopic data,[3] products **3** and **7** were isomeric ketones. These differ only in the size of the heterocycle, the five-membered heterocycle having a carbonyl group on the side chain. The structure of **7** is established by the similarity of the IR- and ^1H NMR spectra of **7** to those of **5** (Table 1); the structure of **3** therefore belongs to the other isomer.

The structures of **3** and **7** were confirmed by their mass spectra. Figure 1 shows that the features of the fragmentations of their molecular ions are quite different and correspond to the assigned structures. So, the existence of peaks corresponding to ions C_5H_{11} (71), COC_5H_{11} (99), ($M\text{-}COC_5H_{11}$) (268) and ($M\text{-}C_5H_{11}$) (296) in the spectrum of **7** testifies to the existence of the acyl [COC_5H_{11}] group in the side chain. In the spectrum of **3**, among the peaks characterizing the side chain of the heterocycle, we distinguished only (C_5H_{11}-H) (70) and ($M\text{-}C_5H_{11}$) (296) which are of very low intensity. The molecular ion of **3** is stabilized quite differently from that of **7**. We assume that it preserves a stable cinnoline fragment MI (242).

Table 1.

Compound	IR, ν_{NH}, cm^{-1}	^1H NMR, δ_{NH}
3	3355	12.95
5	3465	11.55
6	3465	11.45
7	3455	11.75

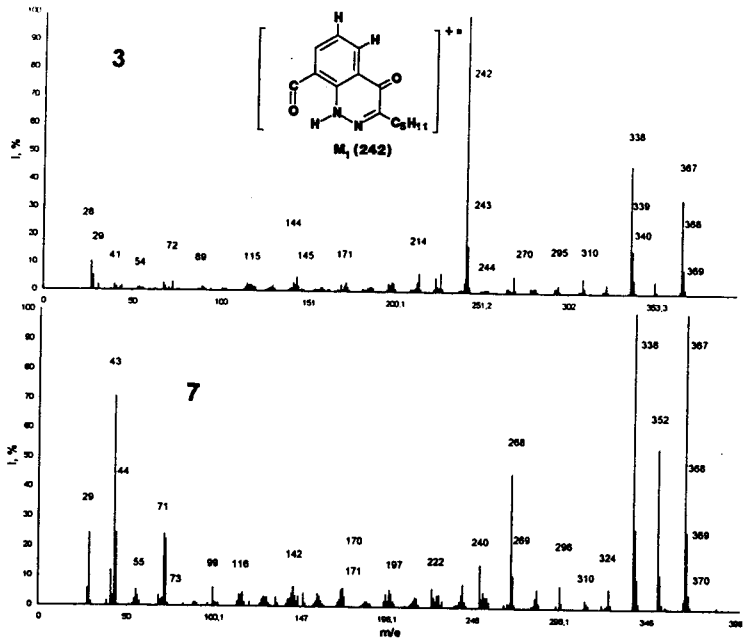
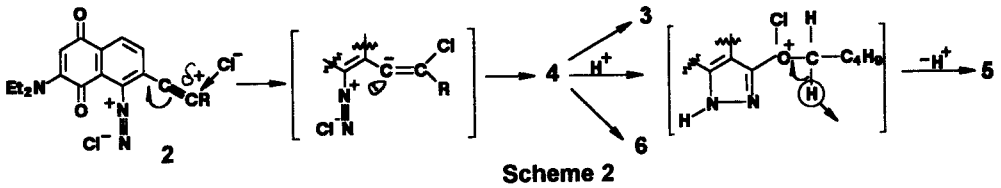


Fig. 1. Mass spectra of isomers **3** and **7**.

We outline possible mechanisms for the heterocyclizations of *ortho*-alkynyl diazonium salts in Scheme 2. The idea is that the triple bond must be modified for participation in cyclization, perhaps by nucleophilic attack on the triple bond. The dependence of the rate of formation of the intermedate on HCl concentration (Cl^- source) is consistent with this assertion. Nucleophilic attack of chloride ion is promoted by the diazo-group which substantially increases the electrophilicity of the acetylenic β-carbon atom. The changes caused by nucleophilic attack favour approach of the reaction centres and their interaction resulting in the formation of the primary cyclization product **4**.

The concentration of the intermediate is determined by the relative rates of its formation and further transformations.



Scheme 2

We suggest that nucleophilic attack on the triple bond, facilitating cyclization, is general for the Richter reaction. Clarification of this question and study of the peculiarities of the chemical conversions of the intermediates are in progress.

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REFERENCES AND NOTES

1. Porter, A.E.A. Diazines and Benzodiazines. In *Comprehensive Organic Chemistry*; Barton, D.H.R.; Ollis, W.D., Eds.; Pergamon Press: Oxford, 1979, Vol.4, pp. 122-124.
2. Shvartsberg, M.S.; Ivanchikova, I.D.; Fedenok, L.G. *Tetrahedron Lett.* **1994**, *35*, 6749-6752.
3. All compounds gave satisfactory analytical and spectroscopic data. ^{1}H NMR spectra for **3-5**, **7** are given below. **3** (m.p. 149-151°C): δ ($CDCl_3$) 0.88 (t, 3H, CH_3), 1.00-1.85 (m, 12H, β-, γ-, δ-CH_2, CH_3CN), 2.85 (t, *J*=8.2 *Hz*, 2H, α-CH_2), 3.55 (q, *J*=7.0 *Hz*, 4H, CH_2N), 5.90 (s, 1H, H^8), 7.97 (d, *J*=7.8 *Hz*, 1H, H^5), 8.60 (d, *J*=7.8 *Hz*, 1H, H^6), 12.95 (br.s, 1H, NH). **4** (m.p. 124-125°C): 0.90 (t, 3H, CH_3), 1.25 (s, 4H, γ-, δ-CH_2), 1.35 (t, *J*=7.0 *Hz*, 6H, CH_3CN), 1.94 (m, 2H, β-CH_2), 3.38 (t, *J*=7.7 *Hz*, 2H, α-CH_2), 3.56 (q, *J*=7.0 *Hz*, 4H, CH_2N), 5.85 (s, 1H, H^7), 8.45 (s, 2H, $H^{4,5}$). **5** (m.p. 114-115°C): 0.95 (t, 3H, CH_3), 1.20-1.70 (m, 12H, β-, γ-, δ-CH_2, CH_3CN), 2.50 (m, 2H, α-CH_2), 3.60 (q, *J*=7.0 *Hz*, 4H, CH_2N), 5.85 (s, 1H, H^7), 6.55 (t, *J*=6.9 *Hz*, 1H, =CH), 7.85 (d, *J*=8.7 *Hz*, 1H, H^4), 8.30 (d, *J*=8.7 *Hz*, 1H, H^5), 11.55 (br.s, 1H, NH). **7** (m.p. 153-155°C): 0.90 (t, 3H, CH_3), 1.00-1.60 (m, 1OH, γ-, δ-CH_2, CH_3CN), 1.80 (m, 2H, β-CH_2), 3.20 (t, *J*=7.2 *Hz*, 2H, α-CH_2), 3.60 (q, *J*=7.0 *Hz*, 4H, CH_2N), 5.88 (s, 1H, H^7), 8.00 (d, *J*=8.2 *Hz*, 1H, H^4), 8.58 (d, *J*=8.2 *Hz*, 1H, H^5), 11.75 (br.s, 1H, NH).