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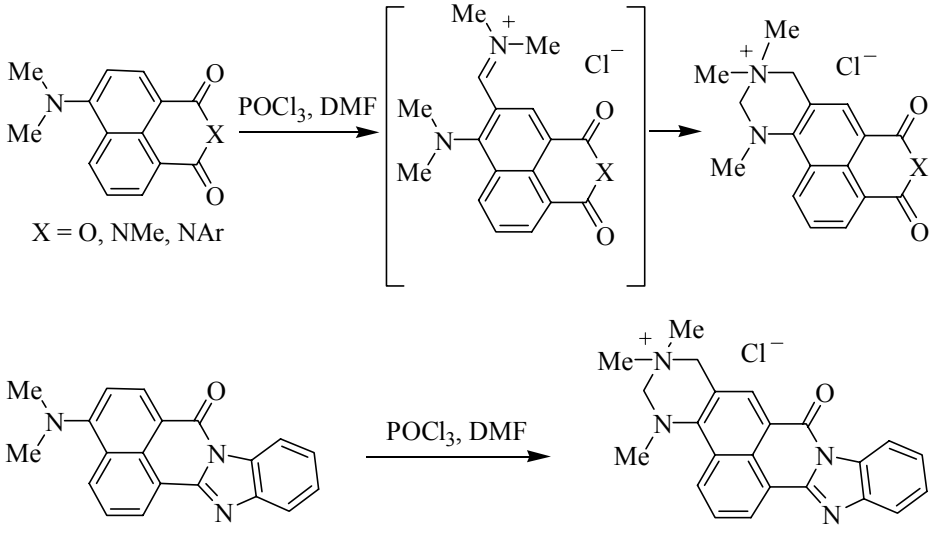
DIMETHYLAMINO-SUBSTITUTED 7H-BENZO[*de*]PYRAZOLO[5,1-*a*]ISOQUINOLIN-7-ONES AND THEIR BEHAVIOR UNDER VILSMEIER–HAACK CONDITIONS

O. N. Lyubenko, I. G. Ermolenko, L. D. Patsenker, B. M. Krasovitskii, and I. N. Tur

The behavior of dimethylamino-substituted 7H-benzo[de]pyrazolo[5,1-a]isoquinoline-7-ones, synthesized for the first time, under conditions of the Vilsmeier–Haack reaction. It has been shown that, on heating with $POCl_3$ and DMF, they are converted by electrophilic substitution at the position ortho to the dimethylamino group, followed by cyclization of the iminium adduct to a quinazolinium salt. When an acetyl group is present, the Arnold reaction, leading to the formation of a chloroaryl, accompanies the heterocyclization. The rates and proportion of the reaction products depend on the position of the dimethyl groups relative to the pyrazole ring.

Keywords: 7H-benzo[*de*]pyrazolo[5,1-*a*]isoquinoline-7-ones, quinazolinium salts, heterocyclization, heterocyclization, the Vilsmeier–Haack reaction.

We have shown previously that the anhydride and imides of 4-dimethylaminonaphthalic acid and 4-dimethylamino-1,8-naphthoylen-1',2'-benzimidazole form quinazolinium salts [2,4] under Vilsmeier–Haack [1] formylation conditions in place of the expected formyl-substituted products.



Institute of Monocrystals, Ukraine National Academy of Sciences, Kharkov 61001, Ukraine; e-mail: patsenker@isc.krarkov.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, 594-603, April, 2003. Original article submitted October 15, 2002.

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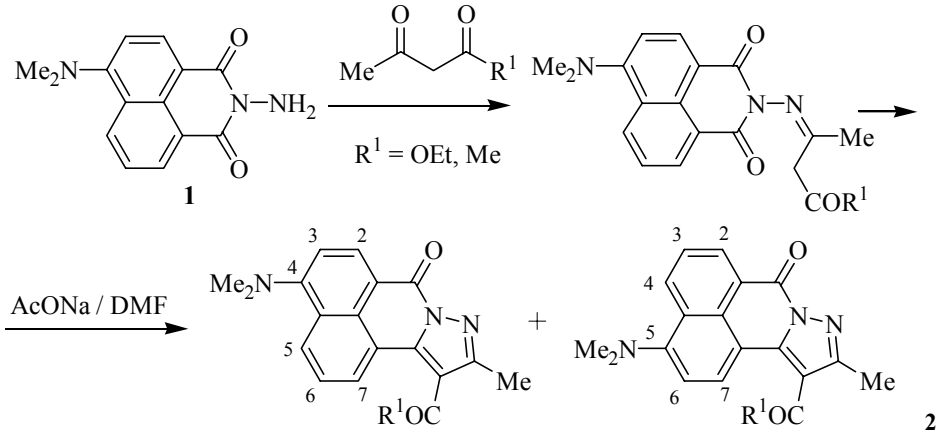
The observed heterocyclization is of interest as an example of the so-called "tertiary-amino group effect" which has not been studied much until now [5, 6]. The mechanism of this reaction has been investigated [7] using quantum-chemical calculations. The quaternary salts formed are stable compounds, intensely fluorescent in solution and in the crystalline state. Consequently they were proposed for practical use as effective water soluble green and yellow luminophores in particular for active lasers and dyes for plastics [8, 9].

The attack of the Vilsmeier complex at the *ortho* position to the dimethylamino group in aromatic compounds does not always give rise to cyclization. For example, 4-dimethylaminobenzonitrile gave the trivial 3-formyl substituent [10], while 6-dimethylamino-2-phenyl-2,3-dihydro-1H-1,3-phenalenedione reacted with elimination of the dimethylamino group [11].

The aim of the present work was to investigate the direction of the reaction with dimethylamino-substituted 7H-benzo[*de*]pyrazolo[5,1-*a*]izoquinolin-7-ones, which had been prepared for the first time and which can be considered as condensed pyrazole derivatives of 4-dimethylaminonaphthalic acids. These compounds were synthesized [12] by the reaction of N-amino imides of 4-dimethylaminonaphathalic acids **1** with ethyl acetoacetate or acetylacetone with yields of 49 and 71% respectively. Subsequent cyclization of the condensation products by refluxing with anhydrous sodium acetate in DMF gave pyrazoles in 85 and 81% yields. The overall yields of the desired compounds calculated on the basis of the initial amino imide was quite satisfactory, corresponding to 42 and 57%. However, the reactions gave two isomeric esters **2a** and **2b** or acetyl-substituted compounds **3a** and **3b** which differ in the position of the dimethylamino groups relative to the carbonyl group. According to ^{1}H NMR spectroscopic data compounds **2a** and **2b** are formed in the ratio of 5:3, while **3a** and **3b** are formed in the ratio of 2:1. Their R_f values are only slightly different but they have different colors in the crystalline state (orange for **2a** and **3a**, red for **2b** and **3b**) and in solution (yellow and orange) and also have different fluorescence maxima. In [12] the similar isomers were not isolated and their mixtures were proposed for dyeing plastics. We have isolated both isomers in pure form by preparative column chromatography and have confirmed their structures by ^{1}H NMR spectroscopy. Unfortunately complete separation was not achieved which reduced the yields of the individual compounds (Table 1).



We then studied the behaviour of the dimethylamino-substituted compounds **2a,b** and **3a,b** under Vilsmeier–Haack conditions. Heating esters **2a** and **2b** with $POCl_3$ in DMF at 100°C gave water soluble compounds which were isolated and identified by ^{1}H NMR spectroscopy as quinazolinium salts with structures **4a** and **4b**. Signals of protons of two methylene groups, a methyl groups bonded to nitrogen, and two methyl groups attached to the quaternary nitrogen atom, which are characteristic of quinazolinium salts, and the absence of the doublet of one of the *ortho* protons of the dimethyllaminophenyl unit, characteristic of the starting materials (Table 2). There was no evidence of the formation of aldehydes in the reaction.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent)	Color of crystals	IR spectrum, ν, cm^{-1}		Yield, %*
		C	H	N	Cl			$C=O_{ester}$	$C=O_{carbonyl}$	
2a	$C_{20}H_{19}N_3O_3$	68.70 / 68.77	5.38 / 5.44	11.60 / 12.03	—	204-205 (benzene)	Orange	1710	1680	18
2b	$C_{20}H_{19}N_3O_3$	68.71 / 68.77	5.40 / 5.44	11.79 / 12.03	—	194-195 (benzene)	Red	1710	1680	12
3a	$C_{19}H_{17}N_3O_2$	71.35 / 71.47	5.24 / 5.33	12.98 / 13.17	—	180-181 (benzene)	Orange	1770	1640	19
3b	$C_{19}H_{17}N_3O_2$	71.33 / 71.47	5.21 / 5.33	12.60 / 13.17	—	194-195 (benzene)	Red	1700	1650	10
4a	$C_{23}H_{25}ClN_4O_3$	62.59 / 62.65	5.73 / 5.67	12.23 / 12.71	7.89 / 8.06	251-252 (ethanol)	Yellow	1700	1680	30
4b	$C_{23}H_{25}ClN_4O_3$	62.59 / 62.65	5.72 / 5.67	12.66 / 12.71	8.23 / 8.06	242-245 (ethanol)	Orange	1690	1650	34
5a	$C_{23}H_{25}F_6N_4O_3P$	50.11 / 50.18	4.46 / 4.54	10.54 / 10.18	—	315-318 (acetonitrile)	Yellow	1700	1680	45

* The yields of compounds **2a,b** and **3a,b** are calculated on the basis of the starting N-amino imide **1**.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

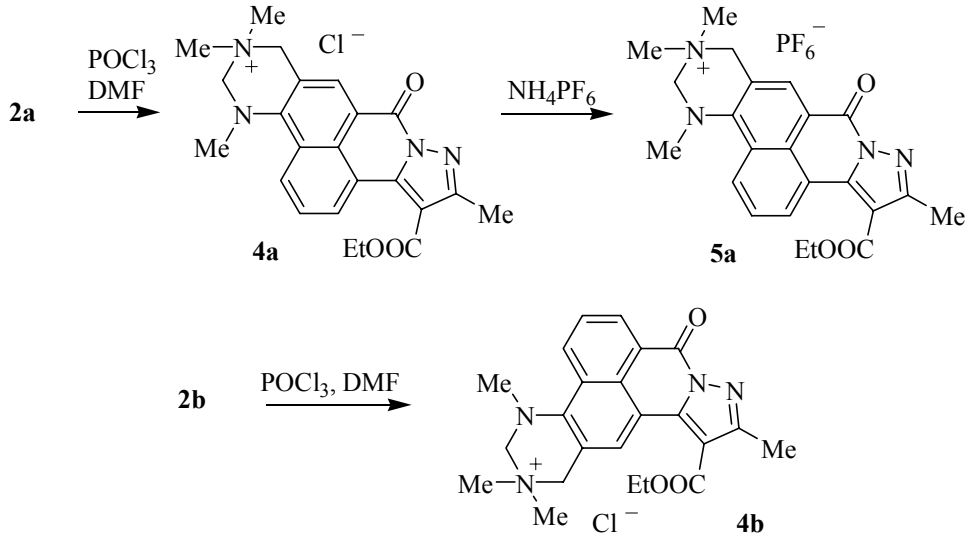
Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
2a	1.39 (3H, t, *J* = 7.2, $COOCH_2\underline{CH_3}$); 2.50 (3H, s, CH_3); 3.19 (6H, s, $N(CH_3)_2$); 4.42 (2H, q, *J* = 14.1, *J* = 7.2; $COO\underline{CH_2}CH_3$); 7.24 (1H, d, *J* = 8.5, 3-H); 7.68 (1H, t, *J* = 8.0, 6-H); 8.38 (1H, d, *J* = 8.5, 5-H); 8.52 (1H, d, *J* = 8.5, 2-H); 9.28 (1H, d, *J* = 7.6, 7-H)
2b	1.39 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 2.48 (3H, s, CH_3); 3.07 (6H, s, $N(CH_3)_2$); 4.38 (2H, q, *J* = 14.2, *J* = 7.1; $COO\underline{CH_2}CH_3$); 7.18 (1H, d, *J* = 8.5, 6-H); 7.83 (1H, t, *J* = 7.9, 3-H); 8.62 (1H, dd, *J* = 8.4, *J* = 0.7; 4-H); 8.68 (1H, d, *J* = 7.3, 2-H); 9.26 (1H, d, *J* = 8.4, 7-H)
3a	2.55 (3H, s, CH_3); 2.67 (3H, s, $COCH_3$); 3.19 (6H, s, $N(CH_3)_2$); 7.26 (1H, d, *J* = 8.5, 3-H); 7.69 (1H, t, *J* = 8.1, 6-H); 8.39 (1H, dd, *J* = 8.5, *J* = 0.9; 5-H); 8.53 (1H, d, *J* = 8.5, 2-H); 8.86 (1H, dd, *J* = 7.7, *J* = 0.8; 7-H)
3b	2.57 (3H, s, CH_3); 2.64 (3H, s, $COCH_3$); 3.07 (6H, s, $N(CH_3)_2$); 7.21 (1H, d, *J* = 8.5, 6-H); 7.86 (1H, t, *J* = 7.9, 3-H); 8.66 (1H, d, *J* = 8.4, 4-H); 8.71 (1H, d, *J* = 7.5, 2-H); 8.98 (1H, d, *J* = 8.5, 7-H)
4a	1.41 (3H, t, *J* = 7.2, $COOCH_2\underline{CH_3}$); 2.49 (3H, s, CH_3); 3.31 (6H, s, $N^+(CH_3)_2$); 3.72 (3H, s, NCH_3); 4.42 (2H, q, *J* = 14.0, *J* = 7.0; $COO\underline{CH_2}CH_3$); 5.02 (2H, s, CH_2); 5.17 (2H, s, CH_2); 7.75 (1H, t, *J* = 8.2, 6-H); 8.32 (1H, s, 2-H); 8.39 (1H, d, *J* = 8.6, 5-H); 9.27 (1H, d, *J* = 7.6, 7-H)
4b	1.41 (3H, t, *J* = 7.2, $COOCH_2\underline{CH_3}$); 2.54 (3H, s, CH_3); 3.30 (6H, s, $N^+(CH_3)_2$); 3.68 (3H, s, NCH_3); 4.41 (2H, q, *J* = 14.1, *J* = 7.2; $COO\underline{CH_2}CH_3$); 4.92 (2H, s, CH_2); 5.11 (2H, s, CH_2); 7.91 (1H, t, *J* = 7.9, 3-H); 8.65 (1H, d, *J* = 6.3, 2-H); 8.68 (1H, d, *J* = 8.2, 4-H); 9.16 (1H, s, 7-H)
5a	1.41 (3H, t, *J* = 7.1, $COOCH_2\underline{CH_3}$); 2.52 (3H, s, CH_3); 3.24 (6H, s, $N^+(CH_3)_2$); 3.69 (3H, s, NCH_3); 4.44 (2H, q, *J* = 14.1, *J* = 7.0; $COO\underline{CH_2}CH_3$); 4.93 (2H, s, CH_2); 5.06 (2H, s, CH_2); 7.84 (1H, t, *J* = 8.1, 6-H); 8.45 (1H, s, 2-H); 8.46 (1H, d, *J* = 7.9, 5-H); 9.36 (1H, d, *J* = 7.6, 7-H)

It should be noted that in the case of a number of anhydrides and imides of 4-dimethylaminonaphthalic acid decribed earlier the heterocyclization reaction occurred very rapidly, in 10-30 min depending on the nature of the "imide" unit [4]. The pyrazoles **2a** and **2b** react considerably more slowly at the same temperature. Complete conversion of the 4-dimethyamino-substituted **2a** required 3 h, while the 5-isomer **2b** was converted into quaternary salt in 4 h. Semi-empirical quantum-chemical calculations using the PM3 method showed that the pyrazole fragment, containing the carbonyl group, has decreased electron density at atom C(6) while that at C(3) is unchanged, Thus the rate of electrophilic substitution at the position *ortho* to the dimethylamino group decreases in parallel with the decreased negative charge in the series: N-methylamide of 4-dimethylaminonaphthalic acid (-0.179 e), > **2a** (-0.169 e) > **2b** (-0.141 e).

As reported previously [3, 4], quinazolinium salts are generally stable in neutral or acid aqueous solutions, but on heating, especially in alkaline media, they are hydrolysed with opening of the heterocycle and elimination of one CH_2 group. This, coupled with their high solubility in water, creates a definite difficulty in isolating the salts from the reaction mixture and in their subsequent purification. Consequently, despite the adequately high yields of the reaction according to ^{1}H NMR spectroscopic data of not less than 55% for **4a** and 68% for **4b**, the valuable salts were isolated in pure form in poor yields (Table 1). Isolation was eased by replacing chloride by hexafluorophosphate. This lowered the solubility of the salts and increased their stability. For example while chloride **4a** was obtained in 30% yield after purification, the hexafluorophosphate **5a** was successfully isolated in 45% yield (Scheme 1).

The influence of the Vilsmeier complex on the acetyl derivatives **3a** and **3b** also gave quinazolinium salts, but the acetyl groups also participated in the reaction. The capability of alkylketones to undergo formylation to give β-chlorovinylaldehydes (the Arnold reaction) is well known and many examples have been studied [13]. According to the generally accepted mechanism of this reaction [13], the first step is enolization of

Scheme 1



the acetyl group, which is then attacked by the Vilsmeier complex to give a β-(N,N-dimethyl)vinyl ketone. This then reacts with a second molecule of the Vilsmeier complex to give a bisiminium chloride which can be hydrolysed to the chloroacrylaldehyde. Bearing in mind that substitution and heterocyclization in the position *ortho* to the dimethylamino groups may occur at any of these stages, a general scheme for the formation of possible reaction products is given in Scheme 2.

Quantum-chemical calculations showed that the negative charge on the carbon atom of the acetyl group of isomer **3a** has approximately the same value as that in the position *ortho* to the dimethylamino group (Fig. 1) which makes electrophilic attack approximately equally probable in the two positions. Enolization leads to a considerable (by 1.7 times) increase in the electron density of the acetyl carbon atom, converting it into a considerably stronger nucleophile. However the probability of forming the enol is very small: its calculated enthalpy of formation ΔH_{form} (5.69 kJ/mol) is considerably higher than for the acetyl form (2.05 kJ/mol). As a

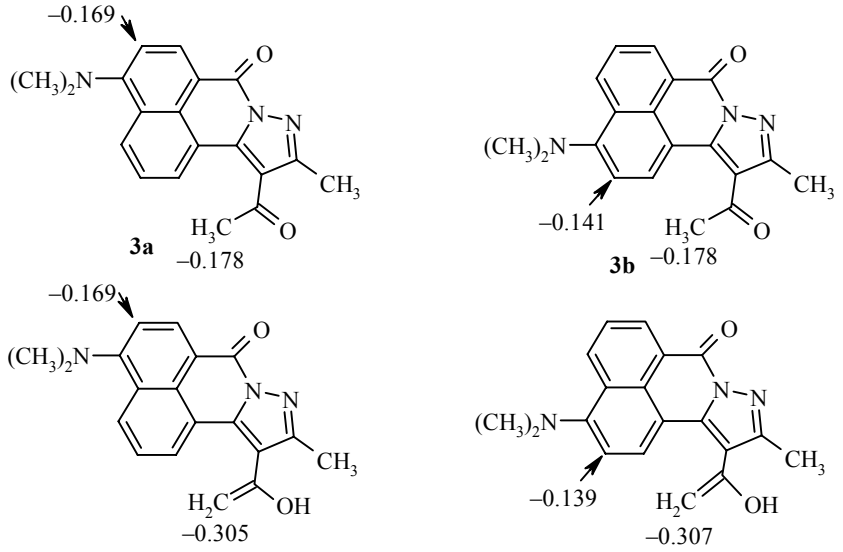
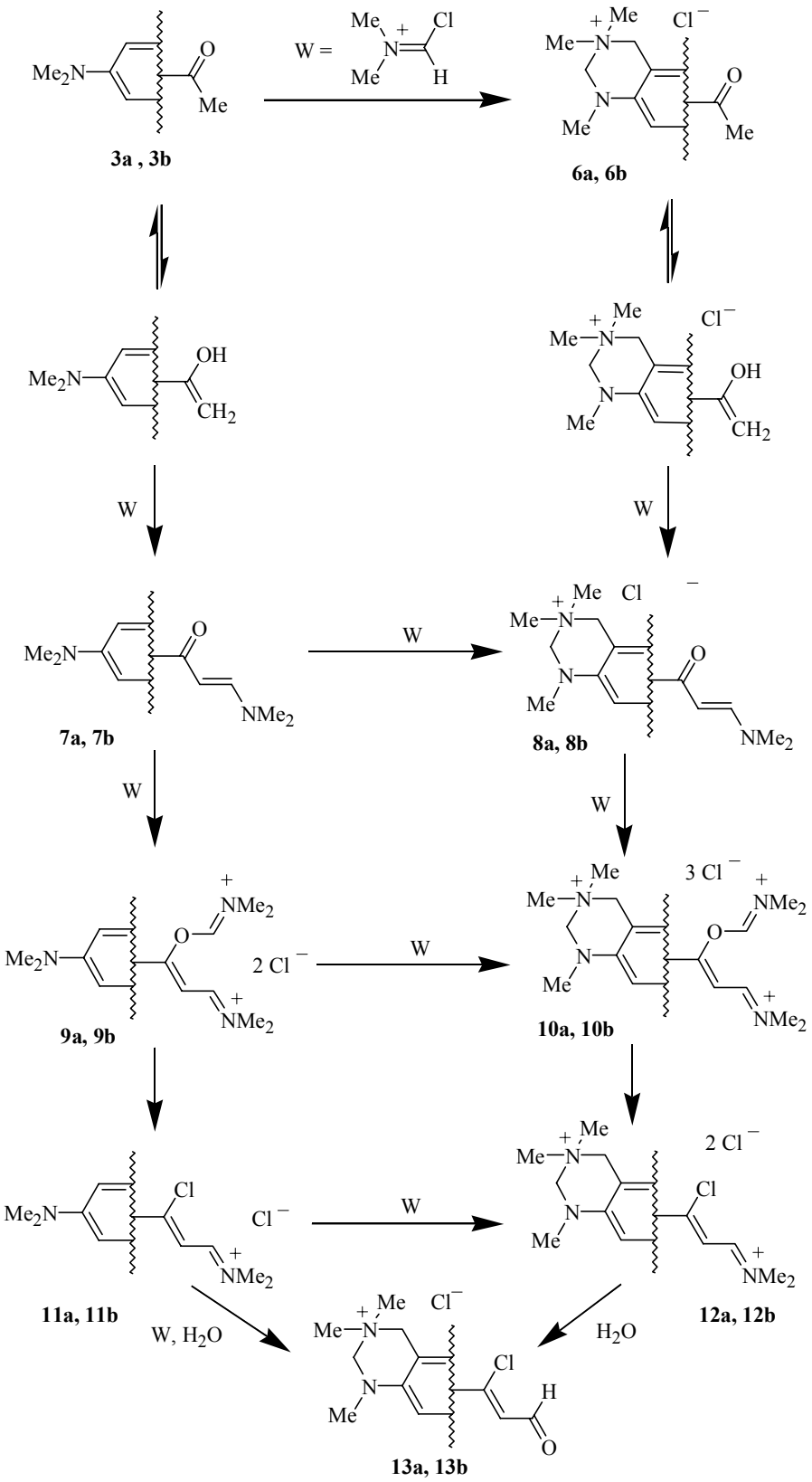


Fig. 1. Charge distribution at the reactive carbon atoms in molecules **3a**, **3b** and their enolized forms.

Scheme 2


W =
3a , 3b
6a, 6b
7a, 7b
8a, 8b
9a, 9b
10a, 10b
11a, 11b
12a, 12b
13a, 13b
W
W, H2O
H2O
2 Cl −
3 Cl −

result the calculated activation barriers for both processes are approximately equal: $\Delta G^{\ddagger}$ for the position *ortho* to the dimethylamino groups is 7.48 kJ/mol, while for attack at the acetyl group it is 7.64 kJ/mol. Consequently it would be expected that with an excess of the formylating agent that formation of the heterocycle and substitution at the acetyl group would be equally likely or that heterocyclization would predominate. It should also be noted that the two reactive positions are well separated from one another and scarcely conjugated. As a result substitution or complex formation at one site should not affect the other. Analysis of the reaction mixture carried out by ^{1}H NMR spectroscopy showed that formation of a considerable amount of the quinazolinium salt began in the first 5 min of the reaction. This compound is easily identified by the signals of the signals of the two methylene groups (5.06 and 4.93), the methylamino group (3.68), and the quaternized dimethylamino group (3.23 ppm). That almost all of the electrophilic substitution occurs at the position *ortho* to the dimethylamino group is also indicated by the observations that the reaction occurs at practically the same rate as for the ester **2a**, and that the non-salt compound **7a** is formed only in trace amounts. After consumption of the starting pyrazole **3a** the quinazolinium salts **6a**, **8a**, and **12a** and the aldehyde **13a** (δ_{CHO} 10.21 ppm) were observed as reaction products.

The isomeric acetyl derivative **3b** reacts analogously. However, as in the case of esters **2a** and **2b**, it reacts about 1.3 times more slowly than compound **3a**, which indicates the decreased rate of substitution in the position *ortho* to the dimethylamino group.. This conclusion is in agreement with the charge distributions in molecules **3a**, **3b** and their enolized forms (Fig. 1): the negative charge on the carbon atom of the acetyl or enolized acetyl groups in both isomers have similar values, but the charge on the position *ortho* to the dimethylamino group drops significantly on going from compound **3a** to compound **3b**. So the calculated results indicate the rate of reaction at the acetyl groups of the two isomers should be practically the same, whereas the attack at position 6 of isomer **3b** is considerably less likely than at position 3 of compound **3a** or at the acetyl group. Such a decrease in the rate of substitution at the position *ortho* to the dimethylamino groups is in fact observed experimentally. Thus, in contrast to isomer **3a**, after 5 min from the beginning of the reaction, apart from the quaternary salts **6b**, **8b**, and **12b**, more than 50% of a non-salt compound was observed, which, according to ^{1}H NMR spectroscopy, was the dimethylaminoethylene derivative **7b**. The content of **7b** originally increased, but then decreased until it had disappeared completely in approximately 3.5-4 h. At the same time the quantities of the quinazolinium salts **6b**, **8b**, and **12b** increased.

Thus, in contrast to the esters **2a** and **2b**, the acetyl derivatives **3a** and **3b** form mixtures of salts with very similar R_f values and solubilties.

Consequently separating them in pure form was unfortunately unsuccessful, but their presence among the reaction products was confirmed by ^{1}H NMR spectroscopy.

EXPERIMENTAL

IR spectra in KBr tablets were measured on a Specord IR-75 spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with HMDS as internal standard were measured with a Varian Mercury VX-200 (200 MHz) instrument. Resonances of isomers **3a** and **3b** were obtained by double resonance of the signals of the acetyl protons. Course of the reactions and the purity of the reaction products were monitored by TLC on Silufol UV-254 strips with 10:1 chloroform–methanol as eluent, and also by ^{1}H NMR spectroscopy. Samples of the reaction mixtures for analysis were first hydrolysed with ice water, neutralised and separated into water soluble and hydrophobic substances by extraction with benzene. The starting compound **1** was synthesized by a known method [14]. Quantum-chemical calculations were carried out with the semi-empirical method PM 3 [15] with complete optimization of the geometry.

General Method for the Synthesis of Ethyl 4-Dimethylamino-10-methyl-7-oxo-7H-benzo[*de*]pyrazolo[5,1-*a*]isoquinoline-11-carboxylate (2a) and Ethyl 3-Dimethylamino-10 methyl-7-oxo-7H-benzo[*de*]pyrazolo[5,1-*a*]isoquinoline-11-carboxylate (2b). A mixture of amino imide **1** (5 mmol), diethyl acetoacetate (4.5 ml, 35 mmol), and *p*-toluenesulfonic acid (0.01 g, 0.057 mmol) was stirred for 4 h under a weak stream of argon at 130°C. After cooling, the precipitated hydrazone was filtered off, washed with methanol and water, and dried. It was then refluxed for 1 h in DMF (2.5 ml) and anhydrous sodium acetate (0.02 g, 0.12 mmol). The precipitate was filtered off, washed with methanol, then water, and dried. The isomers **2a** and **2b** were separated by column chromatography (Al_2O_3, benzene).

General Method for the Synthesis of 1-(4-Dimethylamino-10-methyl-7-oxo-7H-benzo[*de*]pyrazolo[5,1-*a*]isoquinolin-11-yl)-1-ethanone (3a) and 1-(3-Dimethylamino-10-methyl-7-oxo-7H-benzo[*de*]pyrazolo[5,1-*a*]isoquinolin-11-yl)-1-ethanone (3b). A mixture of the amino imide **1** (5 mmol), acetylacetone (1.0 ml, 10 mmol), and *p*-toluenesulfonic acid (0.012 g, 0.68 mmol) in chlorobenzene (5 ml) was refluxed in a Dean–Stark apparatus under argon until water ceased to be evolved. The precipitate formed was filtered off, washed with methanol, then water, and dried. The hydrazone was then refluxed for 1 h in DMF (3 ml) with anhydrous sodium acetate (0.012 g, 0.15 mmol). The precipitate was filtered off washed with methanol, then water, and dried. Isomers **3a** and **3b** were separated by column chromatography (Al_2O_3, benzene).

General Method for Carrying out the Reaction of the Dimethylamino-substituted Compounds 2a, 2b, 3a, and 3b with the Vilsmeier Complex. $POCl_3$ (0.37 ml, 4 mmol for esters **2a** and **2b**, 0.74 ml, 8 mmol for compounds **3a** and **3b**) was added dropwise at 60°C to a mixture of pyrazole **2a**, **2b**, **3a**, or **3b** (1 mmol) in DMF (2 ml, 26 mmol). The mixture was stirred at 100°C for 3 h (isomers **2a** and **3a**) or 4 h (isomers **2b** and **3b**), cooled and poured with stirring into a small amount of ice water. 13-Acetyl-4,6,6,12-tetramethyl-9-oxo-4,6,7,9-tetrahydro-5H-pyrazolo[5',1':1,2]isoquino[4,5-*gh*]quinazolin-6-ium (**4a**) and 12-acetyl-2,2,4,11-tetramethyl-8-oxo-2,3,4,8-tetrahydro-1H-pyrazolo[1',5':2,3]isoquino[4,5-*gh*]quinazolin-2-ium (**4b**) chlorides, and also the mixture of salts from the conversion of compounds **3a** and **3b**, were precipitated from water with 2-propanol. Chlorides **4a** and **4b** were recrystallized from ethanol. Addition to the aqueous solution of $LiPF_6$ (0.15 g, 1 mmol) gave 13-acetyl-4,6,6,12-tetramethyl-9-oxo-4,6,7,9-tetrahydro-5H-pyrazolo[5'.1':1,2]isoquino[4,5-*gh*]-quinazolin-6-ium hexafluorophosphate **5a** which was purified by column chromatography (silochrom C-120, acetonitrile.

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