# SYNTHESIS OF FORMAMIDINES FROM 2-AMINO-3-METHYLQUINAZOLIN-4-ONE AND ITS 6-NITRO DERIVATIVE

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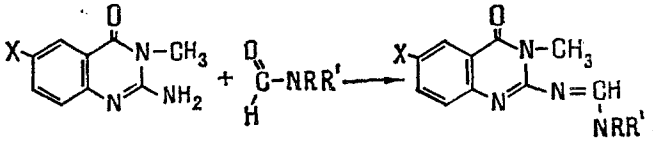
The condensation of 2-amino-3-methylquinazolin-4-one and its 6-nitro derivative with dialkyl-, arylalkyl-, and heterylformamides has given the corresponding formamidines of the quinazolinone series. The details of the compounds synthesized are as follows X, R, R', yield (%), mp (°C, ethanol), $R_f$ (chloroform–methanol (20:1) $Al_2O_3$): empirical formula: H, $CH_3$, $CH_3$, 77, 238-240, 0.49, $C_{12}H_{14}ON_4$; H, $C_2H_5$, $C_2H_5$, 65, 208-210, 0.96, $C_{14}H_{18}ON_4$; H, $CH_3$, $C_6H_5$, 84, 162-164, 0.54, $C_{17}H_{16}ON_4$; H, $(CH_2)_2O(CH_2)_2$, 60, 196-197, 0.43, $C_{14}H_{16}O_2N_4$; H, $(CH_2)_5$, 6.6, 196-198, 0.4, $C_{15}H_{18}ON_4$; $NO_2$, $CH_3$, $CH_3$, 64. 194-196, 0.83, $C_{12}H_{13}O_3N_5$; $NO_2$, $C_2H_5$, $C_2H_5$, 37, 142-144, 0.8, $C_{14}H_{17}O_3N_5$; $NO_2$; $CH_3$, $C_6H_5$, 38, 298, 0.88, $C_{17}H_{15}O_3N_5$; $NO_2$, $(CH_2)_2O(CH_2)_2$, 60, 148-150, 0.7, $C_{14}H_{15}O_4N_5$.

Quinazoline derivatives possess fungicidal [1, 2], herbicidal [3], growth-regulating [4], and other properties, and among formamidines have been found compounds with fungicidal [5], acaricidal [6], ovicidal [7], and repellent [8] activities. Consequently, it appeared of interest to seek biologically active compounds among the quinazolinines containing a formamidine residue. With this aim, and also in continuation of systematic investigations of the synthesis and chemical reactions of quinazolines [9, 10] we have studied for the first time the reaction of 2-amino-3-methylquinazolin-4-one (I) and its 6-nitro derivative (II) with disubstituted formamides.

This reaction is also of interest from the chemical point of view, since it may be expected to take place at two reaction centers: at the exocyclic nitrogen atom and also with the replacement of the hydrogen atom in the aromatic ring. The possibility of the occurrence of the reaction by the latter route was predetermined by the fact that the electrophilic substitution (for example, nitration) of 2-amino-3-methylquinazolin-4-one takes place with the replacement of the hydrogen atom in position 6 of the quinazoline ring. A similar phenomenon has been observed in the nitration of 2,3-polymethylene-3,4-dihydroquinazolin-4-ones [11], which gave 6-nitro-2,3-polymethylene-3,4-dihydroquinazolin-ones.

It has been found that the reaction of (I) and (II) with N, N-disubstituted formamides (IIIa-e) produces 2-N,N-dialkyl-(arylalkyl-, heteryl-)-substituted aminomethyleneaminoquinazolin-4-ones and their nitro derivatives (IV) and (Va-e).



I, II IIIa-e IV, V a-e

I, IV. X=H
II, V. X=$NO_2$

a. R=R'=$CH_3$
b. R=R'=$C_2H_5$
c. R=$CH_3$, R'=$C_6H_5$
d RR'=$(CH_2)_2O(CH_2)_2$
e RR'=$(CH_2)_5$

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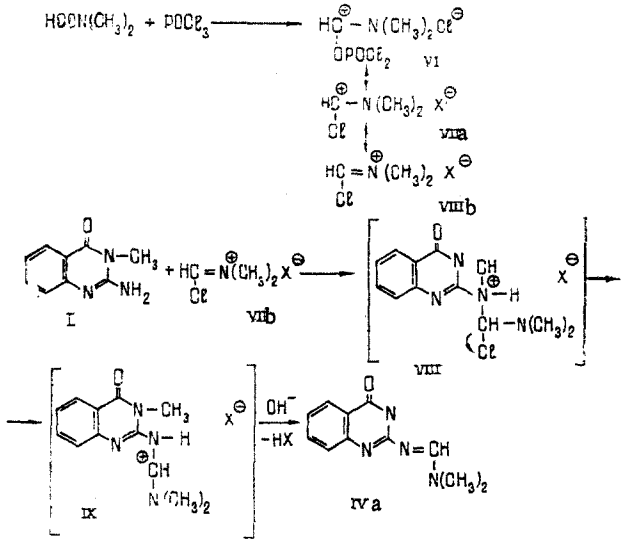
As the formamides we used dimethyl- and diethylformamides (IIIa and b), N-methylformanilide (IIIc), N-formylmorpholine (IIId), and N-formylpiperidine (IIIe). The reactions were carried out with variations in the temperatures, in the ratios of the reactants, and in the time of heating, and in the presence or in the absence of a solvent. They took place best in absolute benzene. It was established that the optimum conditions are quinazolinone:formamide:phosphorus oxychloride ratio 1:2:2; duration of the experiment, 3 h at the boiling point of the reaction mixture. The yields of products amounted to 35-85%. The course of the reaction was followed by chromatography in a thin layer of alumina.

The condensation of 2-amino-3-methylquinazolin-4-one with formamides in the presence of phosphorus oxychloride apparently begins with the formation of an adduct of the disubstituted formamides with the phosphorus oxychloride (VI or VIIa, with dimethylformamide as an example). The complex (VIIa) can exist in the resonance form (VIIb). Subsequently, the amino group of the 2-amino-3-methylquinazolin-4-one nucleophilically attackes the electrophilic reactant (VIIb), which leads to the formation of the intermediate ammonium salt. The splitting out of an HX molecule from the latter compound gives substance (IX), from which, on treatment with a saturated solution of sodium acetate the 2-N-dialkyl-(arylalkyl-, heteryl-) -aminomethylaminoquinazolin-4-ones are formed.



The structures of the compounds synthesized were confirmed by their IR, mass, and NMR spectra, and their individuality was checked by thin-layer chromatography.

The IR spectrum of each of compounds (IV, Va-e$_o$ has absorption bands in the 1610-1690 cm$^{-1}$ region ($\nu_{CN}$, $\nu_{CO}$) and no absorption bands of an amino group. In the spectrum of compound (II), the band characteristic of an amino group appears at 3100 cm$^{-1}$.

The mass spectra of the synthesized compounds each show the strong peak of the molecular ion (83-100%), and also peaks corresponding to the splitting out of the dialkyl-, alkyaryl-, or heterylamine residue; for compounds (II and Vb, c) the splitting out of a NO group is characteristic (M − 30, 20-58%).

In a study of the fungicidal activity of compounds (II-IVa, d, Va-e) it was found that they suppressed the growth of the fungi *Verticillium dahliae* and *Fusarium oxysporum* by 10-40%.

## EXPERIMENTAL

The results of elementary analysis corresponded to the calculated figures. IR spectra were taken on a UR-20 spectrometer, mass spectra on a MK-1303 mass spectrometer, and PMR spectra on a JNM-4H-100 instrument (with HMDS as internal standard).

2-Amino-3-methyl-6-nitroquinazolin-4-one (II). Nitration was carried out as described previously [11]. From 1.75 g (0.01 mole) of 2-amino-3-methylquinazolin-4-one (I) in 42 ml of concentrated $H_2SO_4$ and a nitrating mixture consisting of 2.5 ml of $HNO_3$ (d = 1.5) and 3.5 ml of concentrated $H_2SO_4$ was obtained 2.5 g (95%) of compound (II) with mp 232-234°C (boiling with ethanol). Molecular weight 220, m/e 190 (M − 30), 174 (M − 46). PMR spectrum ($CF_3COOH$),

TABLE 1. Characteristics of the Compounds Synthesized

| Initial compound | Reaction product | R | R' | Yield, % | mp, °C (ethanol) | $R_f$ | mol. wt. (mass spectrum) | Empirical formula |
|---|---|---|---|---|---|---|---|---|
| I | II | — | — | 95 | 232—234 | 0.26 | 220 | $C_9H_8O_3N_4$ |
| I | IVa | $CH_3$ | $CH_3$ | 77 | 238—240 | 0.49 | 230 | $C_{12}H_{14}ON_4$ |
| I | IVb | $C_2H_5$ | $C_2H_5$ | 65 | 208—210 | 0.96 | — | $C_{14}H_{18}ON_4$ |
| I | IVc | $CH_3$ | $C_6H_5$ | 84 | 162—164 | 0.54 | 292 | $C_{17}H_{16}ON_4$ |
| I | IVd | $(CH_2)_5$ | | 6.6 | 196—198 | 0.40 | — | $C_{15}H_{18}ON_4$ |
| I | IVe | $(CH_2)_2O(CH_2)_2$ | | 60 | 196—197 | 0.43 | — | $C_{14}H_{16}O_2N_4$ |
| II | Va | $CH_3$ | $CH_3$ | 64 | 194—196 | 0.83 | — | $C_{12}H_{13}O_3N_5$ |
| II | Vb | $C_2H_5$ | $C_2H_5$ | 37 | 142—144 | 0.80 | 303 | $C_{14}H_{17}O_3N_5$ |
| II | Vc | $CH_3$ | $C_6H_5$ | 38 | 298 | 0.88 | 337 | $C_{17}H_{15}O_3N_5$ |
| II | Vd | $(CH_2)_2O(CH_2)_2$ | | 60 | 148—150 | 0.70 | — | $C_{14}H_{15}O_4N_5$ |

Note. The $R_f$ values were determined in the solvent system chloroform—methanol (20:1) on neutral alumina.

ppm: 3.34 (3 H, singlet), 7.21 (2 H — H8, doublet), 8.18 (2 H — H7, doublet), 8.72 (2 H — H5, doublet). IR spectrum ($cm^{-1}$): 1620, 1685 ($\nu_{CN}$, $\nu_{CO}$), 3100 ($\nu_{NH_2}$).

2-Dimethylaminomethyleneamino-3-methylquinazolin-4-one (IVa). With stirring and cooling 0.4 g (0.02 mole) of 2-amino-3-methylquinazolin-4-one was added to a solution of 0.18 g (0.002 mole) of dimethylformamide in 0.3 g (0.002 mole) of phosphorus oxychloride in 20 ml of absolute benzene. The reaction mixture was stirred at room temperature for 1 h and was then heated in the water bath for 3 h. After cooling, it was treated with a saturated solution of sodium acetate to a neutral reaction and was extracted with chloroform. The chloroform extracts were dried with sodium sulfate, the solvent was distilled off, and the residue was recrystallized from ethanol. This gave 0.4 g of (IVa) with mp 238-240°C. IR spectrum, $cm^{-1}$: 1643, 1690 ($\nu_{CN}$, $\nu_{C=O}$). Molecular weight 230; m/e 176 (M — 54), 175 (M — 55), 159 (M — 71), 147 (M — 83), 146 (M — 84).

2-Diethylaminomethyleneamino-3-methylquinazolin-4-one (IVb). In a similar manner to that described above, 1.0 g (0.12 mole) of N,N-diethylformamide, 1.0 g (0.006 mole) of compound (I), and 0.67 g (0.004 mole) of phosphorus oxychloride in 20 ml of absolute benzene yielded 0.095 g of (IVb) with mp 208-210°C. IR spectrum, $cm^{-1}$: 1615, 1670, 1710 ($\nu_{CO}$, $\nu_{CN}$).

$N^1$-Methyl-$N^2$-(3-methyl-4-oxoquinazolin-2-yl)-$N^1$-phenylformamide (IVc). From 0.5 g (0.003 mole) of (I), 0.4 g (0.003 mole) of N-methylformanilide, and 0.35 g (0.002 mole) of phosphorus oxychloride in 20 ml of absolute benzene was obtained 0.7 g of (IVc) with mp 162-164°C. Molecular weight 292, m/e 277 (M — 15), 221 (M — 71), 200 (M — 92), 160 (M — 132). IR spectrum, $cm^{-1}$: 1620, 1665 ($\nu_{CO,CN}$).

2-Dimethylaminomethyleneamino-3-methyl-6-nitroquinazolin-4-one (Va). From 0.73 g (0.01 mole) of dimethylformamide, 1.1 g (0.005 mole) of 2-amino-3-methyl-6-nitroquinazolin-4-one (II), and 2.3 g (0.015 mole) of phosphorus oxychloride in 20 ml of absolute benzene was obtained 0.9 g of (Va) with mp 194-196°C. IR spectrum, ($cm^{-1}$): 1620, 1635, 1680 ($\nu_{CO,CN}$). PMR spectrum ($CF_3COOH$), ppm: 3.06 (6 H — $N(CH_3)_2$, singlet), 3.38 (3 H — N—$CH_3$, singlet), 7.31-8.24 (3 H, multiplet, aromatic protons).

$N^1$-Methyl-$N^2$-(3-methyl-4-oxo-6-nitroquinazolin-2-yl)-$N^1$-phenylformamidine (Ve). From 0.7 g (0.004 mole) of N-methylformanilide, 0.8 g (0.0036 mole) of 2-amino-3-methyl-6-nitroquinazolin-4-one, and 2.35 g (0.015 mole) of phosphorus oxychloride in 20 ml of pyridine was isolated 0.45 g of compound (Vc) with mp 298°C. Molecular weight 337, m/e 307 (M — 30), 220 (M — 117), 106 (M — 231). IR spectrum, $cm^{-1}$: 1620, 1670, 1690 ($\nu_{CN,CO}$).

2-Diethylaminomethyleneamino-3-methyl-6-nitroquinazolin-4-one. In the way described above, 0.92 g (0.0045 mole) of diethylformamide, 1.0 g (0.0045 mole) of 2-amino-3-methyl-6-nitroquinazolin-4-one, and 2.3 g (0.015 mole) of phosphorus oxychloride in 20 ml of absolute benzene yielded 0.5 g of (Vb) with mp 142-144°C. Molecular weight 303; m/e 288 (M — 15), 273 (M — 30), 231 (M — 72). IR spectrum, $cm^{-1}$: 1620, 1680 ($\nu_{CO,CN}$).

## SUMMARY

It has been shown that the reactions of 2-amino-3-methylquinazolin-4-one and its 6-nitro derivative with dialkyl(arylalkyl-, heteryl-) -formamides form the corresponding formamidines containing the quinazoline ring. The nitration of 2-amino-3-methylquinazolin-4-one

leads to the replacement of the hydrogen in position 6 of the aromatic ring, giving 2-amino-3-methyl-6-nitroquinazolin-4-one.

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# AN INVESTIGATION OF THE VENOM OF RENARD'S VIPER *Vipera ursini renardi*.

## IV. THE HEMOLYTIC ACTION OF THE PHOSPHOLIPASES $A_2$


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The whole venom of the viper and the pure phospholipases $A_2$ isolated from it possess no independent hemolytic action but acquire it in the presence of pure cytotoxins from the venom of the Central Asian cobra. The efficiency of the hemolytic action of the mixture of the venom or the phospholipases $A_2$ with the cytotoxins depends on the concentration and activities of both constituents of the mixture.


Phospholipases A are "indirect" hemolysins, since under physiological conditions they lyse erythrocytes only in the presence of exogenous phospholipids [1]. In the absence of the latter, the lytic action of pure "acid" phospholipases $A_2$ is also manifested under certain extreme conditions in which cells are present [2], and it is also potentiated by the basic membrane-active components contained in the venoms of elapid snakes [3-5]. The lytic effect of phospholipases $A_2$ is obligatorily connected with enzymatic hydrolysis of the phospholipids of the cytoplasmic membrane [6]. It is known that in relation to their capacity for attacking membrane phospholipids and causing cell lysis the phospholipases $A_2$ from various venoms differ considerably [7, 8]. We have shown previously that the phospholipases $A_2$ isolated from the venom of the Central Asian cobra possess no independent hemolytic action but intensify the lysis of erythrocytes caused by membrane-active components — cytotoxins — obtained from the same venom [5]. In the present paper we consider the hemolytic action of pure phospholipases $A_2$ from viper venom.

In contrast to cobra venom, the viper venom possesses no direct hemolytic activity. The incapacity of the venom for directly lysing washed erythrocytes while it exhibits a high phospholipase activity could be explained by the assumption that the viper venom contains no cytotoxins. In actual fact, when whole viper venom together with the cytotoxins from cobra venom was added to washed erythrocytes hemolysis was observed, its degree rising with an increase in the concentration of the venom (Fig. 1a). The efficiency of the hemolytic activity of the mixture of venom with cytotoxins was also determined by the lytic activity of the cytotoxins themselves, and was somewhat greater in the presence of the component Vc5, which corresponded completely to the differences in the independent hemolytic action of the cytotoxins.


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