ACYLATION OF 2-AMINOQUINAZOL-4-ONES BY UNSATURATED ACID CHLORIDES

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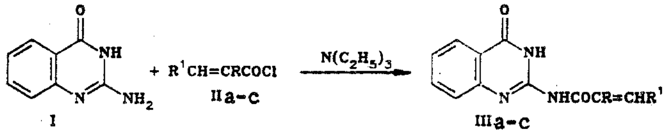
The acylation of 2-aminoquinazol-4-one by unsaturated acid chlorides proceeds principally at the exocyclic nitrogen atom and is complicated in the case of acryloyl chloride by a further intramolecular condensation forming 1,2,3,4-tetrahydropyrimido(2,1-b)quinazolin-2,6-dione. A lower acylation temperature using methacryloyl chloride leads to accumulation of 1-methacryloyl-2-aminoquinazol-4-one in the reaction mixture.

2-Aminoquinazol-4-ones on alkylation and acylation can show a capacity for dual reactions. Alkylation of 2-aminoquinazol-4-ones by unsaturated acids proceeds at the ring N_3 atom [1]. The alkylation products are unstable and undergo intramolecular acylation forming 1,2,3,4-tetrahydropyrimido(2,1-b)quinazolin-2,6-diones.

The aim of the present work is to investigate the acylation of 2-aminoquinazolin-4-one (I) by unsaturated acid chlorides. Alkylation of compound (I) by methacrylic (IIa), crotonic (IIb), and cinnamic (IIc) acid chlorides in the presence of an equimolar quantity of triethylamine in DMF at 80-90°C proceeds selectively at the exocyclic nitrogen atom with formation of 2-acylaminoquinazol-4-ones (IIIa-c).

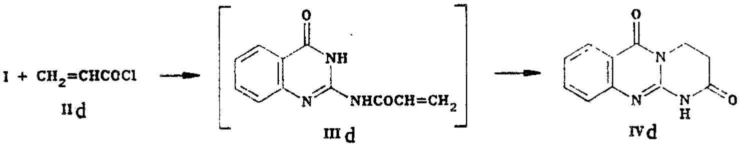


II, III a $R=CH_3$, $R^1=H$; b $R=H$, $R^1=CH_3$; c $R=H$, $R^1=C_6H_5$

The structures of the compounds obtained are confirmed by their mass spectra, in which there is a base peak for the molecular ion, and a fragment ion $[M - NHCOCR{=}CHR^1]^+$ which corresponds to elimination of an exocyclic fragment of the molecule and has an intensity of 60-80% of the base peak. A pathway of this kind involving dissociative ionization is typical for 2-aminosubstituted pyrimidines [2].

Acylation of compounds (IIIa-c) is confirmed by the presence in the IR spectra of three intense bands 1675, 1620 cm^{-1} (C=N, C=C), and a doublet in the region 1760-1690 cm^{-1} (C=O). A multiplet at 5.5-6.4 ppm for (IIIb) and 7.1-7.4 ppm for (IIIa, c) due to the interaction of olefinic protons in the exocyclic fragment of the molecule is the most characteristic feature in the PMR spectrum of acyl derivatives of 1-aminoquinazolin-4-one.

On acylation of 2-aminoquinazol-4-one by acrylic acid (IId) chloride, under analogous conditions to those used for acylation by (IIa-c) chlorides, 1,2,3,4-tetrahydropyrimido(2,1-b)quinazol-2,6-dione (IVd) is isolated as a product of intramolecular condensation of the intermediate 2-acryloylamino quinazol-4-one. Previously, (IVd) was obtained on interaction of (I) with acrylic acid [1].



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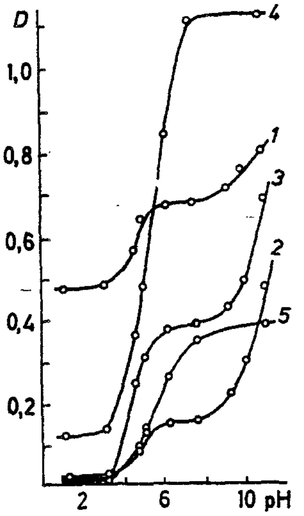
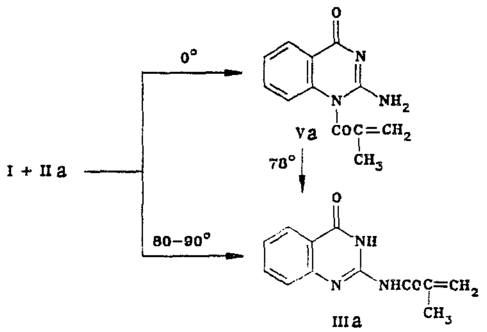


Fig. 1. Dependence of the optical density of solutions of compounds (I), (VI), and (VII) on the pH of the medium. (1) 2-Aminoquinazol-4-one (I), λ 315 nm; (2) (I), λ 330 nm; (3) 2-Methylaminoquinazol-4-one (VI), λ 270 nm; (4) 2-Amino-3-methylquinazol-4-one (VII), λ 265 nm; (5) (VII), λ 330 nm.

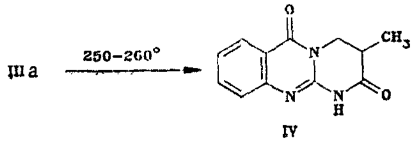
An intense peak for the molecular ion is observed in the mass spectrum of (IVd). The structure of this compound is also demonstrated by the absence of bands in the IR spectrum corresponding to a multiple band stretching vibration. No complex multiplet associated with proton resonance due to the fragment $CH{=}CH_2$, is observed in the region 5.5-6.4 ppm of the PMR spectrum but two triplet signals occur at 2.76 and 4.24 ppm due to methylene protons.

The temperature of acylation of compound (I) by unsaturated acid chlorides has practically no influence on the reaction course except when using (IIa) acid chloride. This was proved by acylation of compound (I) by (IIb, c) acid chlorides at 30°C and 90°C — only compounds (IIIb, c) form as a result. At lower temperatures acylation does not take place. In the case of (IIa) acid chloride, lowering the temperature to 0°C leads to addition of the methacrylic acid residue to the N_1 atom with formation of 1-methacryloyl-2-aminoquinazol-4-one (Va).

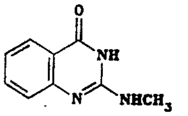


Compound (Va) on heating in alcohol quantitatively isomerizes to (IIIa). Structure (Va) is demonstrated by the lowering of the stretching frequencies of the carbonyl group conjugated with C=N to 1680-1690 cm^{-1} when compared with the spectrum of compound (IIIa). The fragmentation of exocyclic groups is characteristic of the breakdown of compound (Va) on electron bombardment, and by contrast to the spectrum of the isomeric compound (IIIa), intense peaks for fragment ions $[M - CH_2C(CH_3)CO]^+$, $[M - NH_2]$, and $[M - NH - CH_2C(CH_3)CO]^+$ with intensity 15, 10, 85%, respectively, of the base peak are observed in its mass spectrum. Formation of ions $[M - NH_2]^+$ and $[M - NH_2 - CH(CH_3)CO]^+$ proceed successively, as was confirmed by a metastable transition. The anomalous acylation of compound (I) by (IIa) chloride is evidently associated with the higher thermodynamic stability of N_1 acylated (Va) compared with that of compounds (IIIb, c). It was not possible to isolate products due to acylation at the N_1 nitrogen atom for the latter compounds.

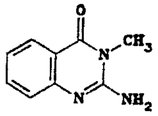
Compound (IIIa) cyclizes on heating forming 3-methyl-1,2,3,4-tetrahydropyrimido(2,1-b)-quinazolin-2,6-dione (IV).



To find an explanation of the course of acylation, we studied the acid-base properties of 2-aminoquinazolone (I) and two of its derivatives methylated at either the exocyclic nitrogen atom (compound (VI)) or N_3 atom (VII).



VI

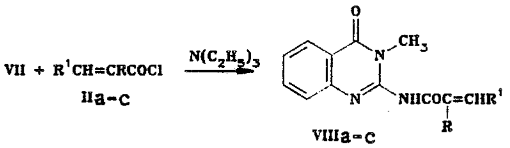


VII

The variation of the optical densities of compounds (I), (VI), and (VII) in buffer solutions over the pH range 1-11 was investigated with this aim in view (see Fig. 1). Changes in the spectra in the alkaline region at pH > 8 are observed only for compounds (I) and (VI), being unsubstituted at the N_3 ring atom. These changes are probably connected with ionization of the amide proton in position 3. An accurate determination of the dissociation constants was hindered by hydrolysis of the compounds, for which the pK_α values are approximately 9.5-10.0.

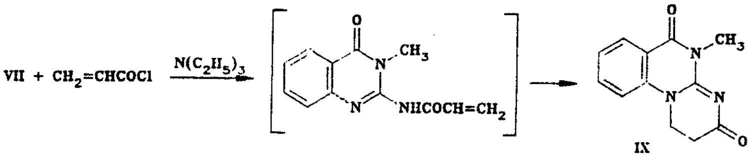
A reversible equilibrium is observed in the range pH 3-6. The variation of the optical density of the solutions with the acidity of the medium has a clearly pronounced sigmoid character. We attribute changes in the spectra to protonation of the ring N_1 atom. The similar pK_{BH^+} values for compounds (I) and (VII) (4.74 ± 0.03 and 4.66 ± 0.05, respectively) are evidence of this; some increase in basicity of the methylamine (VI) (pK_{BH^+} 5.28 ± 0.03) is associated with the inductive effect of the methyl group. The pK_α values for compounds (I), (VI), and (VII) are close to the pK_α of 2-aminoquinazolone (4.82), for which the ring N_1 atom is protonated [3]. This shows that compounds (I), (VI), and (VII) are also protonated at the ring nitrogen atom.

These data concerning the correlation in basicity of nitrogen atoms in the ambident system are not confirmed by the results of acylation of 3-methyl-2-aminoquinazol-4-one (VII) by (IIa-c) chlorides. As in the case of (I), acylation proceeds exclusively with formation of 3-methyl-2-acylaminoquinazol-4-one (VIIIa-c) i.e., the exocyclic nitrogen atom is acylated and not the N_1 ring atom possessing the highest electron density.



Structures (VIIIa-c) are confirmed by their mass spectra in which ion peaks $[M]^+$ and $[M - NHCOR{=}CHR^1]^+$ with intensities of 20 and 60%, respectively, are present.

On acylation of compound (VII) by acrylic acid (IId) chloride, 11-methyl-2,3,4,5-tetrahydropyrimido[2,1-b]quinazolin-2,10-dione (IXd) is formed instead of the expected 3-methyl-2-acryloylaminoquinazol-4-one. The former product results from an intramolecular condensation of the latter intermediate.



N—H and C=C bands in the regions 3170-3220, 1600-1630 cm^{-1} are absent from the IR spectrum of compound (IXd). There is no characteristic multiplet corresponding to fragment $CH{=}CH_2$ in the PMR spectrum; protons for two methylene groups appear as two triplets at 2.95 and 4.51 ppm.

Thus, addition of the acyl function to compounds (I) and (VII) proceeds mainly at the exocyclic amino group.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer (KBr pellets), the PMR spectra on a JNM-4H-100 spectrometer (solvents $CDCl_3$, CF_3COOH, CD_3OD) at 20°C, internal standard TMS.

TABLE 1. Properties of Synthesized Compounds

Compound	T_{mp}, °C	Found, %			Molecular formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIIa	250—251	62,8	4,7	18,4	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	59
IIIb	198—200	62,7	4,9	18,2	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	70
IIIc	395	70,2	4,2	14,3	$C_{17}H_{13}N_3O_2$	70,1	4,1	14,4	36
IVa	272—273	62,6	4,6	18,1	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	15
IVd	250—252	61,2	4,3	19,3	$C_{11}H_9N_3O_2$	61,4	4,2	19,5	43
Va	220	62,6	4,9	18,4	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	20
VI	238—240	61,5	5,1	24,0	$C_9H_9N_3O$	61,7	5,2	23,9	56
VIIa	273—275	61,4	5,0	23,8	$C_9H_9N_3O$	61,7	5,2	23,9	90
VIIIb	220—222	64,3	5,4	17,2	$C_{13}H_{13}N_3O_2$	64,2	5,3	17,3	67
VIIIc	182—183	64,3	5,2	17,4	$C_{13}H_{13}N_3O_2$	64,2	5,3	17,3	49
VIII	132—134	70,6	4,8	13,6	$C_{18}H_{15}N_3O_2$	70,8	4,9	13,7	36
IX	260—262	62,6	4,6	18,1	$C_{12}H_{11}N_3O_2$	62,8	4,8	18,3	15

The mass spectra were obtained on a MX-1303 instrument, with direct introduction of the sample, at an ionizing electron energy of 70 eV. The UV spectra were recorded on a Hitachi ETX-3t instrument (ethanol, buffered solutions). Control of the reaction process and purity of products was effected by TLC on Silufol plates using a chloroform—ethanol (4:1) solvent system. Chromatographic separation of the mixture (IIIa-Va) was carried out on a column (200 × 3) cm containing activated Al_2O_3, grade II, eluent benzene.

2-Aminoquinazolone, 3-methyl-2-aminoquinazol-4-one (VII), and 2-methylaminoquinazol-4-one (VI) were synthesized by methods in [4], [5], and [6] respectively.

2-Methacryloylaminoquinazol-4-one (IIIa). A. Methacrylic acid chloride (10.5 g, 0.01 mole) in DMF (100 ml) is added with stirring to a mixture of 2-aminoquinazol-4-one (I) (16.1 g, 0.01 mole) and triethylamine (10.1 g, 0.1 mole) in DMF (400 ml). The reaction mixture is heated for 6 h at 90°C, then treated with water (100 ml), and the residue removed by filtration. Yield 13.6 g (59%), mp 250-251°C (from ethanol). IR spectrum: (CF_3COOH): 1.28 (3H, d, CH_3); 7.30-7.73 ppm (6H, m, $=CH_2$, C_6H_4). UV spectrum (ethanol), λ_{max} (log ε): 239 (3.87), 276 nm (3.79). Mass spectrum, m/z (%): 229 (M, 110), 214 (20), 201 (15), 200 (30), 187 (15), 161 (25), 145 (60).

Compounds (IIIb, c) are obtained analogously, their properties are presented in Table 1.

B. The acylation of compound (I) is carried out at 0°C, under conditions analogous to those described above. At the end of the reaction, the mixture is treated with water (100 ml), the residue removed by filtration and dissolved in ethanol (70 ml). It is then partitioned on a chromatographic column and eluted with benzene, whereupon compounds (IIIa) (R_f 0.20, chloroform—ethanol 4:1) and 1-methacryloyl-2-aminoquinazol-4-one (Va) (R_f 0.72) are obtained. The ratio (IIIa):(Va) is 1.0:1.7. Yield of compound (Va) 4.9 g (21%). mp 220°C (from ethanol). IR spectrum: 1620 (C=C), 1660 (C=N), 1685 cm (C=O). PMR spectrum (CF_3COOH): 1.10 (3H, d, CH_3); 7.12-8.02 ppm (6H, m, $=CH_2$, C_6H_4). Mass spectrum, m/z (%): 229 (M^+, 100), 214 (10), 161 (15), 146 (85).

1,2,3,4-Tetrahydropyrimido(2,1-b)quinazolin-2,6-dione (IVd). The acid chloride of (IIId), (10.2 g, 0.1 mole) in DMF (100 ml) is gradually added with stirring to a mixture of 2-aminoquinazol-4-one (16.1 g, 0.1 mole) and triethylamine (10.1 g, 0.1 mole) in DMF (350 ml). The reaction mixture is heated for 5 h at 80°C. After treatment with water, the residue is removed by filtration. Yield 9.2 g (43%). mp 250-252°C (from ethanol). No mp depression was observed on admixture with compound (IVd) obtained previously [1].

Compound (IVa) is obtained analogously on heating (IIIa) at 250-260°C without a solvent.

3-Methyl-2-methacryloylaminoquinazol-4-one (VIIIa) is synthesized and separated analogously to compound (IIIa) from 3-methyl-2-aminoquinazol-4-one (VII) and the methacrylic acid (IIa) chloride. Yield 67%. mp 220-222°C (from ethanol). IR spectrum: 1630 (C=C), 1670 (C=N), 1700 cm^{-1} (C=O). UV spectrum (ethanol), λ_{max} (log ε): 230 (3.99), 274 nm (3.64). PMR spectrum (CF_3COOH): 2.0 (3H, s, CH_3); 3.8 (3H, s, NCH_3); 5.6-6.4 (3H, m, CH=CH); 7.3-8.4 ppm (4H, m, C_6H_4). Mass spectrum, m/z (%): 243 (M, 20), 159 (60). Compounds (VIIIb, c) are obtained analogously. Their properties are presented in Table 1.

11-Methyl-2,3,4,5-tetrahydropyrimido(2,1-b)quinazolin-2,10-dione (IX). The acid chloride of (IId) (0.9 g, 0.01 mole) in DMF (70 ml) is added with stirring to a mixture of 3-methyl-2-aminoquinazol-4-one (1.6 g, 0.01 mole) and triethylamine (1.0 g, 0.01 mole) in DMF (100 ml). The mixture is heated for 7 h at 90°C, then treated with water (100 ml). Yield 0.33 g (14%). mp 260-262°C (from ethanol). IR spectrum: 1635 (C=N), 1695 cm^{-1} (C=O). PMR spectrum (CF_3COOH): 3.0 (2H, t, $COCH_2$); 3.55 (3H, s, CH_3); 4.50 ppm (2H, t, NCH_2). UV spectrum (ethanol), λ_{max} (log ε): 230 (3.03), 255 (3.32), 282 (4.3) nm. Mass spectrum, m/z (%): 229 (M, 100), 201 (50).

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REACTION OF 2,4,6-TRIPHENYLVERDAZYL WITH TRIFLUOROMETHYLSULFONYLCARBETHOXYDIBROMOMETHANE

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and V. I. Staninets

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An unusual acylation of 2,4,6-triphenylverdazyl by trifluoromethylsulfonylcarbethoxydibromomethane in benzene has been discovered leading to 1-ethoxalyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-sym-tetrazine (1-ethoxalyl-2,4,6-triphenylleukoverdazyl).

Formation of 1-acyl-2,4,6-triaryl-1,2,3,4-tetrahydro-sym-tetrazine has been postulated in the reaction of 2,4,6-triarylverdazyl with benzoyl peroxide [1] but the isolation of materials with this structure has not proved successful up to this time. We have found that 2,4,6-triphenylverdazyl (I) reacts with trifluoromethylsulfonylcarbethoxydibromomethane (II) in benzene at 20°C to give a small yield of the known 1,3-diphenyl-5-carbethoxy-1,2,4-triazole (IV) but a 96% yield of the acylation product from I, i.e., 1-ethoxalyl-2,4,6-triphenyl-1,2,3,4-tetrahydro-sym-tetrazine (V) (1-ethoxalyl-2,4,6-triphenylleukoverdazyl). The structure was confirmed by elemental analysis, spectral data, and chemical reactions.

The PMR spectrum of V showed three multiplets for the three phenyl groups at 7.73, 7.34, and 7.02 ppm (15 H) and the ethyl group was identified by a triplet at 1.22 and a quartet at 4.32 ppm. The signals for the geminal methylene group of the tetrazine heterocycle were at 5.13 and 6.16 ppm with J_{AB} = 13.5 Hz. Such a spectral pattern is typical of leukoverdazyls and is explained by substituent inversion at N_2 [2]. The structure is further confirmed by molecular ion (M^+) fragmentation and by IR spectroscopy. The first stage of dissociation of M^+ (m/z 414) involves elimination of the $COCO_2C_2H_5$ radical to form a fragment with m/z 313. The ethoxalyl fragment further loses acetaldehyde to form $HO^+{=}C{=}C{=}O$ (m/z 57). The presence of two carbonyls in V was seen by IR. Evidently the acylating agent is a product of the reaction of reagent II. To investigate the source of oxygen in the acyl fragment of V the experiment was carried out in a Warburg [3] manometric apparatus and also in an

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