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SYNTHESES BASED ON FURANCARBOXYLIC ACID AMIDES.

1. SYNTHESIS AND STRUCTURE OF 2-(5-R-2-FURYL)-4-OXOQUINAZOLINES

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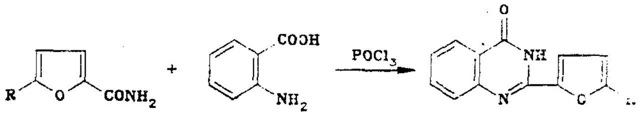
2-(5-R-2-Furyl)-4-oxoquinazolines are formed in the condensation of furancarboxylic acid primary amides with anthranilic acid in the presence of phosphorus oxychloride. It was determined by x-ray diffraction analysis, IR and PMR spectroscopy, and mass spectrometry that a labile hydrogen atom is bonded to the nitrogen atom in the 3-position and that the molecule has an s-NH,O-trans conformation.

Compounds with pronounced biological activity are found in the oxoquinazolines series [1-4]. Little-investigated oxoquinazolines that contain a furan fragment in their structures are of interest in this respect.

The aim of the present research was the synthesis of 2-(5-R-2-furyl)-4-oxoquinazolines on the basis of furancarboxylic acid primary amides and the study of their structures.

2-(5-R-2-Furyl)-4-oxoquinazolines IIa-h (Table 1) were obtained in high yields by condensation of 5-R-furan-2-carboxylic acid primary amides Ia-h with anthranilic acid in the presence of phosphorus oxychloride.



I a-h

II a-h

I, II a R=H, b R=CH$_3$, c R=C$_6$H$_5$, d R=Br, e R=I, f R=NO$_2$, g R=4-BrC$_6$H$_4$, h R=4-NO$_2$C$_6$H$_4$

Oxoquinazoline IIa (Fig. 1, Table 2) was subjected to an x-ray diffraction study to establish the structures of the synthesized compounds.

Compound IIa exists in the form of the s-N,O-trans isomer. The quinazoline ring is planar within the limits of 0.02 Å. The deviation of the $O_{(4)}$ atom from the mean plane drawn through the $N_{(1)}C_{(2)}N_{(3)}C_{(4)}-C_{(10)}$ atoms is 0.7 Å. The maximum deviation of the ring atom from the mean plane of the five-membered heteroring is 0.003 Å for the $O_{(2)}$ atom. The geometry

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TABLE 1. Characteristics of IIa-h

Compound	Empirical formula	mp, °C (T_{dec}, °C)	IR spectrum, cm^{-1}		PMR spectrum, ppm				Yield, %
			C=O	NH	3-H, d (J = 4.0 Hz)	4-H, d	R—H	H_{arom}, m	
IIa	$C_{12}H_8N_2O_2$	220 ... 221	1705	1515, 3435	6,88	6,17	7,23 dd	7,35 ... 8,08	73
IIb	$C_{13}H_{10}N_2O_2$	247 ... 248	1690	1530, 3220	7,72	6,22	2,15 s	7,37 ... 8,06	74
IIc	$C_{18}H_{12}N_2O_2$	(140)	1700	1530, 3210	7,12	6,32	6,73 ... 8,10 m	6,73 ... 8,10	95
IId	$C_{12}H_7BrN_2O_2$	135 ... 137	1705	1530, 3220	7,73	6,50	—	7,25 ... 8,10	64
IIe	$C_{12}H_7IN_2O_2$	(270)	1680	1520, 3210	6,89	5,97	—	7,23 ... 8,11	62
IIf	$C_{12}H_7N_3O_4$	295 ... 297	1710	1550, 3220	7,66	6,98	—	7,27 ... 8,18	93
IIg	$C_{18}H_{11}BrN_2O_4$	(200)	1690	1550, 3215	6,77	6,37	7,07 ... 8,12 m	7,07 ... 8,12	98
IIh	$C_{18}H_{11}N_3O_4$	(160)	1710	1535, 3220	7,13	6,70	7,55 ... 7,95 m	7,55 ... 7,95	98

TABLE 2. Coordinates of the Atoms ($\cdot 10^4$; $\cdot 10^3$ for the H atoms) and Equivalent Isotropic Thermal Parameters of IIa

Atom	X	Y	Z	×10³, Å	Atom	X	Y	Z	×10³, Å	Atom	X	Y	Z	×10³, Å
$N_{(1)}$	5612(3)	5823(1)	8220(2)	52(1)	$C_{(8)}$	5261(5)	6873(1)	8629(3)	62(1)	$H_{(3)}$	203(4)	495(1)	600(2)	80(6)
$C_{(2)}$	4708(4)	5335(1)	7531(2)	47(1)	$C_{(9)}$	4370(4)	6343(1)	7860(2)	51(1)	$H_{(5)}$	−44(4)	688(1)	575(3)	94(7)
$N_{(3)}$	2627(3)	5308(1)	6476(2)	50(1)	$C_{(10)}$	2267(4)	6358(1)	6799(2)	51(1)	$H_{(6)}$	117(4)	777(1)	702(2)	90(7)
$C_{(4)}$	1280(4)	5799(1)	6066(2)	53(1)	$C_{(11)}$	5905(4)	4771(1)	7838(2)	48(1)	$H_{(7)}$	474(4)	778(1)	891(2)	82(6)
$O_{(4)}$	−628(3)	5751(1)	5145(2)	65(1)	$O_{(2)}$	8012(3)	4803(1)	8866(2)	57(1)	$H_{(8)}$	684(4)	686(1)	936(3)	94(7)
$C_{(5)}$	1111(5)	6897(1)	6481(3)	68(1)	$C_{(12)}$	8829(5)	4233(1)	8999(3)	58(1)	$H_{(12)}$	1035(5)	417(1)	969(3)	66(8)
$C_{(6)}$	2027(6)	7412(1)	7246(4)	77(1)	$C_{(13)}$	7317(5)	3856(1)	8116(3)	61(1)	$H_{(13)}$	748(5)	341(1)	800(2)	72(7)
$C_{(7)}$	4075(5)	7396(1)	8316(3)	72(1)	$C_{(14)}$	5420(4)	4200(1)	7361(3)	56(1)	$H_{(14)}$	406(3)	407(1)	665(3)	76(7)

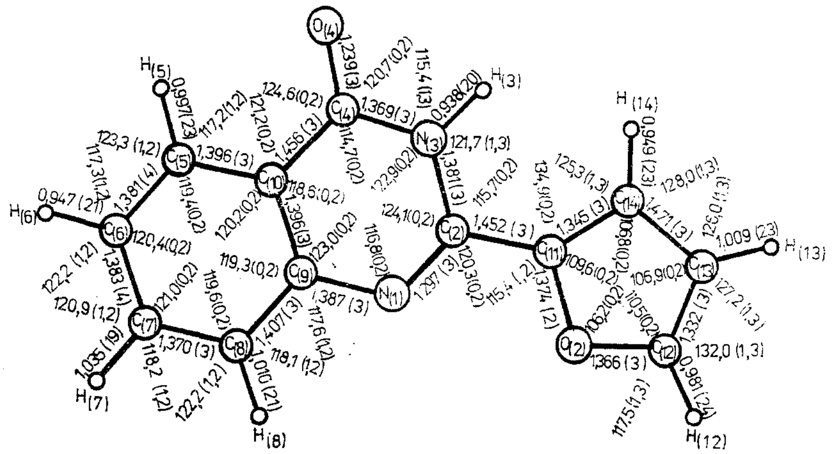


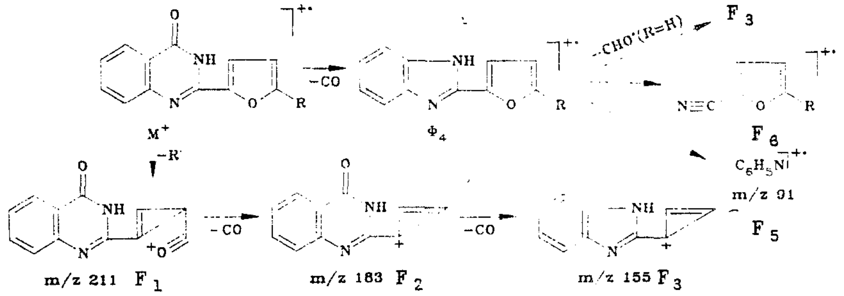
Fig. 1. Structure of the 2-(2-furyl)-4-oxoquinazoline molecule, bond lengths, and bond angles.

of the furan fragment bonded to the 4-oxoquinazoline ring basically coincides with that established for the furan molecule [5]. The angle between the heterorings is 2.1°, and, consequently, the molecule as a whole is planar. The substantial shortening of the $C_{(2)}-C_{(11)}$ bond as compared with the standard length of the C–C bond (1.54 Å) and, in addition, the lengthening relative to the C=C bond (1.336 Å) [6] constitute evidence for the existence of conjugation between the heterorings. In the quinazoline fragment the $N_{(3)}-C_{(2)}$ bond is shortened as compared with the standard R_2NH length, which is equal to 1.472 Å [7], whereas the $C_{(4)}-N_{(3)}$ and $N_{(1)}-C_{(2)}$ bonds are longer than the standard values of the amide C–N (1.333 Å and C=N (1.255 Å [6] bonds, respectively, which indicates participation of the unshared electron pairs of the nitrogen atoms in the conjugation system. In the unit cell of the crystal the molecules are packed in the form of centrosymmetric dimers formed due to an $NH_{(3)}\ldots O_{(4)}$ intermolecular hydrogen bond, which is equal to 1.936 Å and corresponds to the standard value of 1.94 Å [7].

The IR spectra of IIa and IIb-h (Table 1) have general character and include bands of stretching vibrations of a secondary amide group. At 1608-1620 cm^{-1} one finds a band of stretching vibrations of the C=N group of the oxoquinazoline ring, the intensity of which virtually is not inferior to that of the absorption band of the C=O group. On passing from the solid phase to solution ($CHCl_3$) one observes shifts of the absorption bands of the C=O bond and the deformation vibrations of the NH group to the high-frequency region of 15-20 cm^{-1} and 220-250 cm^{-1}, respectively, as well as a 15-25 cm^{-1} shift of the band of stretching vibrations of the NH group to the low-frequency region, which may be associated with cleavage of the intermolecular hydrogen bonds.

In the PMR spectra of II recorded in trifluoroacetic acid the signal of the NH proton is found at 9.70-9.80 ppm. The chemical shifts and the spin–spin coupling constants (SSCC) of the furan and oxoquinazoline rings (Table 1) are typical.

Scheme



The fragmentation of the molecular ions of IIa, d (see the scheme) involves the competitive cleavage of the furan and oxoquinazoline rings and the formation of even-numbered-electron (F_1-F_3) and odd-numbered-electron (F_4-F_6) fragments (Table 3). Fragments F_1-F_3 arise as a result of the successive splitting out of radical R and the subsequent elimination of two

TABLE 3. Mass Spectra of IIa and IId

Compound	W_M	Intensities of the ion peaks in percent relative to the maximum						
		M^+	F_1	F_2	F_3	F_4	F_5	F_6
IIa	10,0	100	14	18	7	6	6	14
IIb	5,6	100	22	32	35	25	19	44

molecules of CO. The splitting out of a molecule of CO from the oxoquinazoline ring leads to the formation of cation radical F_4, the subsequent fragmentation of which takes place via the pathways that are customary for benzimidazoles.

EXPERIMENTAL

The IR spectra of suspensions of the compounds in mineral oil and solutions in chloroform were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were recorded with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The mass spectra were obtained with a Varian MAT-112 chromatographic mass spectrometer at an ionizing-electron energy of 70 eV with direct introduction of the samples into the source.

For the x-ray diffraction study we selected a crystal of acicular form with dimensions of 0.12 mm by 0.20 mm by 0.05 mm. The crystals were monoclinic and had the following parameters: a = 4.859(3), b = 22.30(2), c = 8.945(5) Å, $\gamma = 94.49(5)^\circ$, $\nu = 966(1)$ Å^3, $d_{calc} = 1.46$ g/cm^3, $F_{000} = 400$, space group $P2_{1/b}$, Z = 4(1). The set of structural amplitudes from 916 reflections with I > 3 (I) was obtained with a Nicolet P3 x-ray diffractometer in Mo K_α emission with a graphite monochromator. All of the calculations were made with a NOVA3 computer by means of a set of SHELXTL programs [9]. The structure was solved by the direct method and was refined within the anisotropic (isotropic for the H atoms) approximation up to R = 0.029 with $R_w = 0.031$.

The results of elementary analysis of IIa-h for C, H, N, and Hal were in agreement with the calculated values.

2-(2-Furyl)-4-oxoquinazoline (IIa). A solution of 2.22 g (0.02 mole) of furan-2-carboxylic acid amide and 2.74 g (0.02 mole) of anthranilic acid in 7.5 ml of phosphorus oxychloride was heated for 1 h at 100°C. After the reaction mixture was cooled to room temperature, the excess phosphorus oxychloride was decomposed with water, and the precipitated crystals were removed by filtration, washed with water, dried, and recrystallized from ethanol—dioxane (1:1) to give 3.23 g (73%) of IIa.

Compounds IIb-h were similarly synthesized.

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