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THE SERIES OF 3H-QUINAZOL-4-ONE.

XIV. SYNTHESIS AND PROPERTIES OF 1-ETHOXALYL(METHOXYSUCCINYL)-3-ARYL-1,2,3,4-TETRAHYDROQUINAZILIN-3-ONES

O. E. Sattarova, Yu. V. Kozhevnikov, V. S. Zalesov, S. N. Nikulina, and N. V. Semyakina

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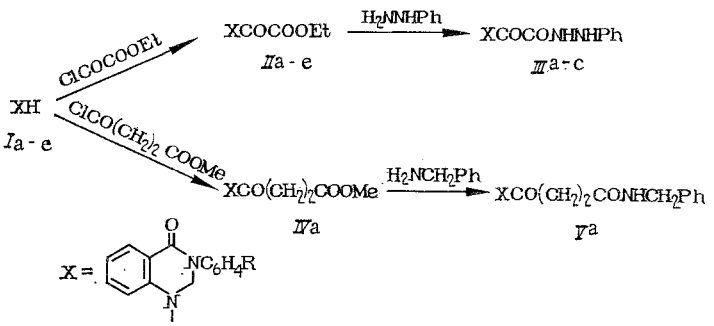
In a search for biologically active compounds, and in continuation of the investigation in [2], we obtained a series of derivatives of 1-ethoxalyl(methoxysuccinyl)-3-aryl-1,2,3-4-tetrahydroquinazolin-4-ones according to the following scheme:



I — V: R = H (a), Me = 2 (b), Br = 4 (c), Me = 4 (d), OMe = 4 (e)

In the reaction of 3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (Ia-e) with oxalic acid monoester chloride or β-carbomethoxypropionyl chloride, 1-ethoxalyl-3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (IIa-e) and 1-methoxysuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IVa) respectively, were obtained. The reaction of compounds IIa-c with phenylhydrazine leads to the formation of 4-phenylhydrazooxalyl-3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (IIIa-c). In the reaction of IVa with benzylamine, 1-benzylaminosuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (Va) was obtained.

The compounds obtained (see Table 1) are crystalline substances, slightly basic in character. They are insoluble in water, but are soluble in ethanol, benzene, toluene, and dioxane. The structure of the compound was confirmed by IR, UV, and PMR spectra, and also by the data of elemental analysis. In the IR spectra of all the compounds there are bands characteristic of the quinazolone ring: at 1650-1660, 1600-1610, 1490-1520 cm^{-1} [4]. In the IR spectra of compounds IIa-e and IVa, intense absorption bands have been observed, due to the presence of an ester group, while for compounds IIIa-c and Va, absorption bands at

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TABLE 1. 1-Ethoxalyl(methoxysuccinyl)-3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calc., %		IR spectrum, ν, cm^{-1}
			Br	N		Br	N	
IIa	80	95—7	—	8,91	$C_{18}H_{16}N_2O_4$	—	8,63	1740, 1680, 1620, 1480, 1430, 1350, 1290, 1220, 1200
IIb	85	93—5	—	8,41	$C_{19}H_{18}N_2O_4$	—	8,28	1740, 1680, 1610, 1480, 1440, 1350, 1300, 1200
IIc	72	100—1	19,7	7,1	$C_{18}H_{15}BrN_2O_4$	19,82	6,95	1750, 1670, 1610, 1500, 1440, 1350, 1200
IId	75	113—5	—	8,4	$C_{19}H_{18}N_2O_4$	—	8,28	1750, 1680, 1610, 1520, 1480, 1410, 1350, 1320, 1200
IIe	78	104—6	—	7,82	$C_{19}H_{18}N_2O_5$	—	7,9	1750, 1680 1600, 1520, 1490, 1420, 1350, 1260, 1200
IIIa	35	280—2	—	14,38	$C_{22}H_{18}N_4O_3$	—	14,5	3300, 3170, 1650, 1620, 1460, 1380, 1260
IIIb	30	264—6	—	14,12	$C_{23}H_{20}N_4O_3$	—	13,99	3330, 3180, 1670, 1650, 1600, 1460, 1380, 1230
IIIc	60	259—61	17,09	11,96	$C_{22}H_{17}BrN_4O_3$	17,17	12,04	3310, 3180, 1680, 1660, 1620, 1500, 1490, 1390, 1280, 1240
IVa	73	114—6	—	8,1	$C_{19}H_{17}N_2O_4$	—	8,28	1740, 1680, 1620, 1480, 1420, 1400, 1350, 1220 1200
Va	60	161—3	—	10,23	$C_{25}H_{22}N_3O_3$	—	10,16	3300, 1650, 1510, 1470, 1440, 1340, 1260

Note. Compounds IIa, c-e, IV, and Va crystallize from ethanol, IIb from toluene, IIIa-c from dioxane.

3170-3300 cm^{-1} due to νNH are characteristic [7]. The UV spectra of the compounds are characterized by the presence of two absorption maxima: at 216-229 and 277-282 nm; compound Va has an absorption maximum at 340 nm. Signals are observed in the PMR spectra of the compounds that confirm their structure.

EXPERIMENTAL CHEMISTRY

The IR spectra were recorded on the UR-20 spectrophotometer (GDR) in the form of a suspension in mineral oil, and the UV spectra on the SF-16 spectrophotometer for $1 \cdot 10^{-5}$ M solutions, using 96% ethanol as solvent. The PMR spectra were run on the PC-60 spectrometer, with TMS as inner standard.

1-Ethoxalyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IIa). A 1.64-g portion (12 mmoles) of monoethyl oxalate chloride is added to a suspension of 2.24 g (10 mmoles) of Ia in 40 ml of benzene, and the mixture is heated on a water bath for 30 min. Benzene is distilled off, the residue is poured into 50 ml of water, and the mixture is neutralized with Na_2CO_3 to a slightly alkaline reaction. After 24 h, the precipitate is filtered, dried, and crystallized. PMR spectrum (CCl_4, δ, ppm): 1.13 m (OCH_2CH_3, 3H), 4.13 q (OCH_2CH_3, 2H), 5.4 s (CH_2, 2H), 7.26 m (phenyl 9H).

Compounds IIb-e are obtained in a similar way.

1-Phenylhydrazooxalyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IIIa). A 2.16-g portion (20 mmoles) of phenylhydrazine in 10 ml of absolute ethanol is added to a solution of 3.24 g (10 mmoles) of IIa in 20 ml of absolute ethanol, and the mixture is left to stand for two days at room temperature. The precipitate is filtered, dried, and crystallized. PMR spectrum [$(CD_3)_2SO$], δ, ppm: 10.4 s (NH–NH, 2H), 7.03 m (phenyl, 14H).

Compounds IIIb, c were obtained in a similar way.

1-Methoxysuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IVa). This is obtained by the same method as IIa, using β-carbomethoxypropionyl chloride as the reagent. PMR spectrum ($CDCl_3$, δ, ppm): 2.63 s (CH_2CH_2, 4H), 3.5 s (CH_3, 3H), 5.4 s (CH_2, 2H), 7.56 m (phenyl, 9H).

1-Benzylaminosuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (Va). A 1.28-g portion (12 mmoles) of benzylamine is added to 2.03 g (6 mmoles) of IVa, and the mixture is held at 19°C for 1 h. The mixture is then cooled and the precipitate recrystallized.

EXPERIMENTAL BIOLOGY

We studied the antimicrobial [3] and antispasmodic activity by carrying out the maximal electroshock test [5] with compound IIa-e, IIIa, b, IVa, and Va, and the acute toxicity [3] of compounds IIb and IIIb, without calculating the LD_{50}. The pharmacological studies were carried out on white mice of both sexes, weighing 18-22 g each. The compounds were introduced intraperitoneally in a 2% starch mucilage. The results were treated statistically by the method of Litchfield and Wilcoxon at P = 0.05 [1]. According to maximal electroshock test, compound IIb had antispasmodic activity. Its activity is lower by a factor of 2.9 than that of the known preparation Chloracon. In a dose of 600 mg/kg, compound IIIb protected 33.3% of the animal from the extensor phase of convulsive fits. Taken in a dose of 60 mg/kg, the remaining compounds did not exhibit antispasmodic action. In a dose of 1000 mg/kg, compounds IIb and IIIb do not cause changes in the behavior of the animals, and according to the Sidorov classification are practically nontoxic.

The antimicrobial activity of the compounds was studied by the method of double serial dilutions in a liquid culture medium on two types of microorganisms (*Staph. aureus* 209P and *E. coli*). We used a meat-peptone bouillion for the cultivation. The microbial charge consisted of $2.5 \cdot 10^5$ cells per 1 ml of the medium. The activity of the compounds was estimated from the value of the minimal bacteriostatic concentration, expressed in microorganisms per ml. Compounds IIIa, b, IVa, and Va have an antimicrobial activity at a concentration of 500 to 1000 μg/ml. At a concentration of 1000 μg/ml, the remaining compounds do not exhibit an inhibiting action towards the two types of the microorganisms.

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