SYNTHESIS AND PROPERTIES OF 2-ISOPROPYL-3-ARYL-4-QUINAZOLONES

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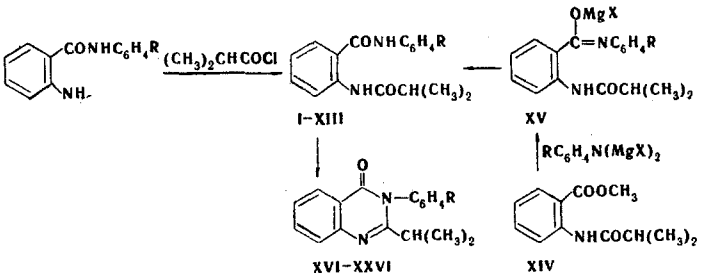
A number of N-isobutyrylanthranilic acid arylamides (I) were obtained. Under the influence of phosphorus trichloride, I are cyclized to 2-isopropyl-3-aryl-4-quinazolones. The UV and IR spectra and biological activity of the quinazolone compounds were studied.

Substances with soporific and antispasmodic activity are found among 2,3-disubstituted 4-quinazolones [1,2], in connection with which a study of the cyclization of N-isobutyrylanthranilic acid arylamides to 2-isopropyl-3-aryl-4-quinazolones is of interest in the development of the research in [3].

N-Isobutyrylanthranilic acid arylamides (I-XIII, Table 1) were obtained by acylation of anthranilic acid arylamides [4] with isobutyryl chloride; in addition, they can be obtained by the reaction of methyl N-isobutyrylanthranilate (XIV) with dimagnesylamines (XV):



Arylamides I-XIII are colorless, crystalline substances of neutral character that are soluble in organic solvents.

When solutions of I-XIII in toluene are heated with phosphorus trichloride, they cyclize to 2-isopropyl-3-aryl-4-quinazolones (XVI-XXVI, Table 2). It was found that arylamides with substituents in the o or m position in the amide group cyclize to give only low yields. In this connection, the reaction of 6-oxo-2-isopropyl-4,5-benzo-1,3-oxazine (XXVII) with arylamines was used to obtain quinazolone compounds of this type.

Quinazolone compounds XVI-XXVI are colorless, crystalline substances with lower melting points than the starting arylamides. They have weak basic properties and form perchlorates.

The structure of the compounds was confirmed by the UV and IR spectra. The UV absorption spectra of XX and XXI are characterized by three maxima and differ substantially from the UV spectra of starting arylamides VI and VII. The well-studied bands characteristic for secondary amides at 1640 and 1570 cm^{-1} [5], which vanish in the spectra of the corresponding quinazolone compounds, are observed in the IR spectra of the arylamides. Bands at 1668-1681 cm^{-1} ($\nu_{C=O}$) and at 1575-1640, 1566-1580, and 1505-1549 cm^{-1} (the latter can probably be ascribed to vibration of the quinazolone ring [6]) are observed in the IR spectra of the quinazolone compounds.

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TABLE 1. N-Isobutyrylanthranilic Acid Arylamides (I-XIII)

Comp.	R	mp, °C (from ethanol)	Empirical formula	N, % found	N, % calc.	Yield, %
I	H	187—188	$C_{17}H_{18}N_2O_2$	9,7	9,9	70
II	*o*-CH_3	136—137	$C_{18}H_{20}N_2O_2$	9,3	9,4	57
III	*m*-CH_3	151—152	$C_{18}H_{20}N_2O_2$	9,3	9,4	80
IV	*p*-CH_3	158—159	$C_{18}H_{20}N_2O_2$	9,5	9,4	61
V	*o*-Br	133—134	$C_{17}H_{17}BrN_2O_2$	8,0	7,8	63
VI	*m*-Br	173—174	$C_{17}H_{17}BrN_2O_2$	7,7	7,8	76
VII	*p*-Br	214—215	$C_{17}H_{17}BrN_2O_2$	8,0	7,8	80
VIII	*o*-Cl	136—137	$C_{17}H_{17}ClN_2O_2$	8,6	8,8	64
IX	*m*-Cl	172—173	$C_{17}H_{17}ClN_2O_2$	8,9	8,8	68
X	p-Cl	199—200	$C_{17}H_{17}ClN_2O_2$	8,6	8,8	78
XI	*o*-CH_3-p-Br	138—139	$C_{18}H_{19}BrN_2O_2$	7,2	7,5	65
XII	*o,p*-$(CH_3)_2$	175—176	$C_{19}H_{22}N_2O_2$	9,1	9,0	77
XIII	*p*-CH_3O	165—166	$C_{18}H_{20}N_2O_3$	9,0	9,0	77

TABLE 2. 2-Isopropyl-3-aryl-4-quinazolones (XVI-XXVI)

Comp.	R	mp, °C base	mp, °C perchlorate	Empirical formula	N, % found	N, % calc.	Yield, %
XVI	H	142—143	241—242	$C_{17}H_{16}N_2O$	10,4	10,6	48
XVII	*m*-CH_3	153—154	242—244	$C_{18}H_{18}N_2O$	10,4	10,1	46
XVIII	*p*-CH_3	145—146	173—175	$C_{18}H_{18}N_2O$	9,9	10,1	45
XIX	*o*-Br	126—127	260—261	$C_{17}H_{15}BrN_2O$	8,1	8,2	31
XX	*m*-Br	139—140	—	$C_{17}H_{15}BrN_2O$	7,9	8,2	30
XXI	*p*-Br	169—170	241—243	$C_{17}H_{15}BrN_2O$	8,3	8,2	54
XXII	*o*-Cl	107—108	218—219	$C_{17}H_{15}ClN_2O$	9,5	9,4	22
XXIII	*m*-Cl	142—143	—	$C_{17}H_{15}ClN_2O$	9,3	9,4	33
XXIV	*p*-Cl	139—140	258—260	$C_{17}H_{15}ClN_2O$	9,5	9,4	29
XXV	*o*-CH_3-p-Br	158—159	240—241	$C_{18}H_{17}BrN_2O$	7,6	7,8	41
XXVI	*p*-CH_3O	175—176	225—227	$C_{18}H_{18}N_2O_2$	9,2	9,5	35

*IR spectrum, cm^{-1}: XIX 1681, 1575, 1558, 1547; XX 1668, 1574, 1543; XXI 1667, 1575, 1505; XXII 1679, 1577, 1560; XXIII 1670, 1580, 1562, 1549; XXIV 1670, 1578, 1562, 1549.

Pharmacological tests demonstrated that quinazolone compounds XVI, XIX, XXIII, and XXVI have tranquilizing, weak soporific, and antispasmodic action, and their activity decreases in the order XIX > XVI > XXIII > XXVI.*

EXPERIMENTAL

6-Oxo-2-isopropyl-4,5-benzo-1,3-oxazine (XXVII). A mixture of 20.7 g (0.1 mole) of isobutyrylanthranilic acid and 40 ml (0.4 mole) of acetic anhydride was refluxed for 1 h. The acetic anhydride was removed by distillation, and the residue was vacuum-distilled to give 16 g (85%) of a product with bp 132-134° (5 mm) and mp 47-48°. IR spectrum: 1726 ($\nu_{C=O}$), 1250, 1180 (ν_{C-O}) cm^{-1}. Found: C 69.7; H 5.8; N 7.2%. $C_{11}H_{11}NO_2$. Calculated: C 70.0; H 5.9; N 7.4%.

Methyl N-Isobutyrylanthranilate (XIV). A 19-g (0.18 mole) sample of isobutyryl chloride was added with stirring to a solution of 27 g (0.175 mole) of methyl anthranilate in 150 ml of ether, and the mixture was allowed to stand overnight. It was then treated with 10% sodium carbonate solution until it was weakly alkaline to litmus. The ether layer was separated, and the aqueous layer was extracted repeatedly with 150 ml of ether. The ether extracts were dried with calcined sodium sulfate, the ether was removed by distillation, and the residue was vacuum-distilled to give 24 g of a product with bp 158-160° (10 mm) and n_D^{40} 1.5410. Found: C 65.1; H 6.8; N 6.2%. $C_{12}H_{15}NO_3$. Calculated: C 65.3; H 6.8; N 6.3%.

N-Isobutyrylanthranilic Acid m-Bromophenylamide (VI). A. A 1.2-g (0.01 mole) sample of isobutyryl chloride was added to a solution of 2.91 g (0.01 mole) of anthranilic acid m-bromophenylamide in 7 ml of pyridine, and the mixture was allowed to stand for 30 min, after which it was diluted with 50 ml of water. The resulting precipitate was crystallized to give 2.7 g (75%) of product.

*The investigations were carried out by N. E. Kharchenko under the supervision of Professor V. M. Grishina.

B. A 6.9-g (0.04 mole) sample of m-bromoaniline in 15 ml of ether was added to ethylmagnesium bromide, obtained from 8.7 g (0.08 mole) of ethyl bromide and 2 g (0.08 g-atom) of magnesium in 30 ml of ether, and the mixture was heated for 20 min on a water bath. A 4.4-g (0.02 mole) sample of XIV in 10 ml of ether was then added, and the mixture was heated for 30 min and decomposed with ammonium chloride solution. The ether layer was separated, the ether was removed by steam distillation, and the residue was crystallized to give 4 g (55%) of product. UV spectrum, λ_{max} (log ε): 258 nm (4.3). IR spectrum: 1640, 1559, 1300 cm^{-1} (amide I and II). This product did not depress the melting point of the compound obtained via method A. Compounds I-XIII were similarly obtained (Table 1).

2-Isopropyl-3-(m-bromophenyl)-4-quinazolone (XX). A. A 1.4-g (0.01 mole) sample of phosphorus trichloride in 5 ml of toluene was added to a solution of 3.6 g (0.01 mole) of VI in 30 ml of toluene, and the mixture was refluxed for 1 h. It was then treated with 15 ml of 10% sodium carbonate solution and steam-distilled. The residue was crystallized from ethanol to give 0.8 g (23.5%) of product.

B. A 3-g (0.017 mole) sample of m-bromoaniline and 1.6 g (0.012 mole) of phosphorus trichloride were added to a solution of 2.9 g (0.015 mole) of XXVII in 20 ml of toluene, and the mixture was refluxed for 1 h and worked up as in experiment A to give 1.5 g (30%) of product. UV spectrum, λ_{max}, nm (log ε): 234 (4.3), 268 (4.1), and 305 (3.8). This product did not depress the melting point of the compound obtained via method A. Compounds XVI-XXVI (Table 2) were similarly obtained. The perchlorates were obtained by addition of 70% perchloric acid to a solution of the base in glacial acetic acid.

The UV spectra of 10^{-5} M alcohol solutions were obtained with an SF-4 spectrophotometer at layer thicknesses of 1 cm. The IR spectra of mineral-oil suspensions were recorded with an IKS-14 spectrophotometer.

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