SYNTHESIS AND BIOLOGICAL ACTIVITY OF 2-METHOXY- AND 2-PHENOXYMETHYL-3-ARYL-4-QUINAZOLONES

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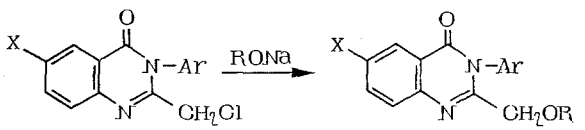
Compounds with soporific and antispasmodic activity are found in the 2,3-disubstituted 4-quinazolone series [1, 2]. It was therefore of interest to obatin a number of 2-methoxy- and 2-phenoxymethyl-3-aryl derivatives of 4-quinazolone in order to reveal their soporific and antispamodic activity. The compounds were synthesized by the scheme:



I *II-XIX*

The starting 2-chloromethyl-3-aryl-4-quinazolones (I) were obtained by cyclization of the corresponding arylamides of N-chloroacetylanthranilic acid by a previously developed method [3]. The chlorine in the chloromethyl group of (I) is activated by the quinazolone ring and therefore readily enters into neucleophilic substitution reactions. When (I) is heated with sodium methoxide in absolute methanol or with phenol in dimethylformamide, 2-methoxy- and 2-phenoxymethyl-3-aryl-4-quinazolones (II)-(XIX) are obtained in 34-90% yields (see Tables 1 and 2). The structure of the quinazolone compounds was confirmed

TABLE 1. 2-Methoxymethyl-3-aryl-4-quinazolones

Compound	R	Ar	X	Yield %	mp	N found %	Empirical formula	N calc. %
II	CH_3	C_6H_5	H	65	182—3 from ethanol	10,30; 10,36	$C_{16}H_{14}N_2O_2$	10,52
III[2]	CH_3	2-$CH_3C_6H_4$	H	35,7	163—4 from methanol	9,70; 9,82	$C_{17}H_{16}N_2O_2$	9,99
IV	CH_3	4-$CH_3C_6H_4$	H	90	164—5 from methanol	10,15; 10,18	$C_{17}H_{16}N_2O_2$	9,99
V	CH_3	2-ClC_6H_4	H	80	137—8 from methanol	9,10; 9,17	$C_{16}H_{13}ClN_2O_2$	9,31
VI	CH_3	4-ClC_6H_4	H	60	185—6 from ethanol	9,17; 9,21	$C_{16}H_{13}ClN_2O_2$	9,31
VII	CH_3	2-BrC_6H_4	H	58	156—7 from methanol	8,37; 8,39	$C_{16}H_{13}BrN_2O_2$	8,11
VIII[2]	CH_3	4-BrC_6H_4	H	87	146—8 from methanol	8,24; 8,30	$C_{16}H_{13}BrN_2O_2$	8,11
IX	CH_3	2-CH_3-4-BrC_6H_3	H	75	148—9 from ethanol	7,61; 7,70	$C_{17}H_{15}BrN_2O_2$	7,79
X	CH_3	4-$CH_3OC_6H_4$	H	82	195—6 from ethanol	9,40; 9,60	$C_{17}H_{16}N_2O_3$	9,45
XI	CH_3	4-ClC_6H_4	Br	34	128—9 from methanol	7,40; 7,50	$C_{16}H_{12}BrClN_2O_2$	7,38

*According to [5], mp 180-181°C.

†IR spectra (in cm^{-1}): (III) 1682, 1635, 1583, 1516; (VIII) 1686, 1624, 1565, 1490.

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TABLE 2. 2-Phenoxymethyl-3-aryl-4-quinazolones

Compound	R	Ar	X	Yield %	Mp	N found %	Empirical formula	N calc. %
XII	C_6H_5	C_6H_5	H	82,2	133—4 (from ethanol)	8,40; 8,45	$C_{21}H_{16}N_2O_2$	8,53
XIII	C_6H_5	$2\text{-}CH_3C_6H_4$	H	57	119—20 (from ethanol)	8,37; 8,41	$C_{22}H_{18}N_2O_2$	8,18
XIV	C_6H_5	$4\text{-}CH_3C_6H_4$	H	42	116—7 (from ethanol)	8,08; 8,13	$C_{22}H_{18}N_2O_2$	8,18
XV	C_6H_5	$2\text{-}ClC_6H_4$	H	55,6	130—1 (from methanol)	7,70; 7,86	$C_{21}H_{15}ClN_2O_2$	7,72
XVI	C_6H_5	$2\text{-}BrC_6H_4$	H	62,5	117—9 (from ethanol)	7,00; 7,14	$C_{21}H_{15}BrN_2O_2$	6,88
XVII	C_6H_5	$4\text{-}BrC_6H_4$	H	83,5	124—5 (from methanol)	6,90; 7,03	$C_{21}H_{15}BrN_2O_2$	6,88
XVIII	C_6H_5	$2\text{-}CH_3\text{-}4\text{—}BrC_6H_3$	H	43	152—3 (from methanol)	6,53; 6,60	$C_{22}H_{17}BrN_2O_2$	6,65
XIX	C_6H_5	C_6H_5	Br	80	171—2 (from methanol)	6,91; 7,12	$C_{21}H_{15}BrN_2O_2$	6,88

Note: IR spectra (in cm^{-1}): (XIII) 1688, 1587, 1498; (XVII) 1674, 1583, 1488.

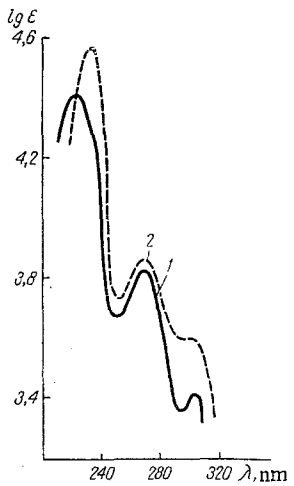

Fig. 1. UV spectra: 1) 2-methoxymethyl-3-(2'-chlorophenyl)-4-quinazolone (V); 2) 2-phenoxymethyl-3-(2'-chlorophenyl)-4-quinazolone (XV).

by counter synthesis in the case of compound (XII) [4] as well as by the UV and IR spectra. The UV spectra of (V) has three absorption maxima at 224-234, 268, and 290-300 nm (see Fig. 1). Intense bands in the region of the Ar—C=O valence vibrations (1682-1688 cm^{-1}) as well as three quinazolone bands are observed in the IR spectra of (III), (VIII), (XIII), and (XVII) [6].

The compounds obtained were investigated for their soporific and antispasmodic activity. The experiments were carried out on white mice. The compounds were introduced intraperitoneally in a 2% starch mucilage as a suspension in 25-300 mg-doses per 1 kg of animal body weight. The soporific activity was determined by the "side position" test. It was found that compounds (V), (VII), (IX), (XIII), (XV), and (XVI) have soporific activity. Compound (V) had especially pronounced soporific activity with an ED_{50} of 35 mg/kg, while the ED_{50} of the remaining compounds was 150-300 mg/kg.

The antispasmodic activity was determined by the "maximum electroshock" test [7]. All the compounds had antispasmodic activity which was manifested 1 h after introduction of doses which were two to three times smaller than the soporific doses. Compounds (III), (V), and (XIII) were the most active. The ASD_{50} (antispasmodic dose, median) of (V) was 26.5 mg/kg.

EXPERIMENTAL

The IR spectra of the compounds were obtained with an IKS-14 spectrophotometer. The samples were prepared as mulls in mineral oil. The UV spectra were obtained with an SF-4 spectrophotometer using 96% ethanol as solvent (C $1 \cdot 10^{-5}$ M).

2-Methoxymethyl-3-phenyl-4-quinazolone (II). A solution of sodium methoxide, prepared from 0.28 g of sodium and 20 ml of absolute methanol, was added to a suspension of 2.7 g of 2-chloromethyl-3-phenyl-4-quinazolone in 50 ml of absolute methanol, and the resulting mixture was refluxed for 5 h. The methanol was then removed, 50 ml of water was added to the residue, and the mixture was neutralized with acetic acid until a weakly acidic reaction to litmus was obtained. The precipitate was filtered, washed with water, dried, and crystallized. Compounds (III)-(XI) were similarly obtained.

2-Phenoxymethyl-3-phenyl-4-quinazolone (XII). Phenol (1.2 g) and 1 g of potassium carbonate were added to a solution of 2.7 g of 2-chloromethyl-3-phenyl-4-quinazolone in 10 ml of dimethylformamide. The mixture was heated on a water bath for 1 h and then poured into 100 ml of water. The precipitate was

filtered, washed with water, dried, and crystallized. No melting point depression was observed for a mixture of this product with the substance obtained by another method [4]. Compounds (XIII)-(XIX) were similarly obtained.

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