SYNTHESIS AND PHARMACOLOGICAL INVESTIGATIONS OF SOME QUINAZOLONE DERIVATIVES

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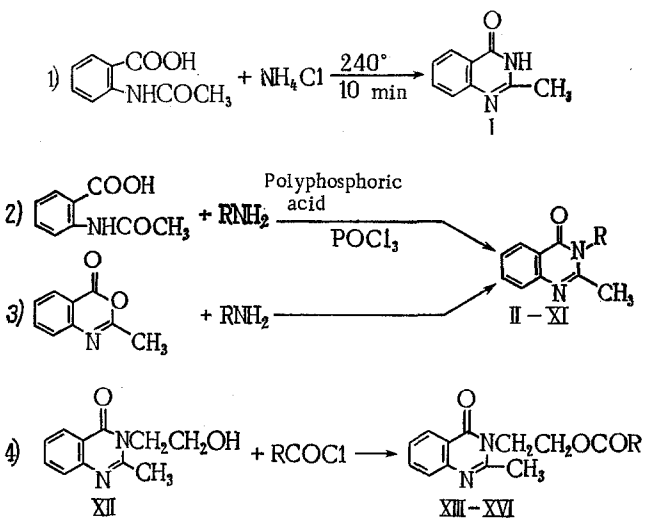
Compounds having antimalarial activity along with compounds possessing soporific activity have been found among quinazolone derivatives. The high soporific activity of Motolon, 2-methyl-3-(o-tolyl)-4-quinazolone, and also the literature data concerning the various pharmacological activities of 2-methyl-4-quinazolones substituted in the third position compelled us to investigate in more detail the relationship between the structure and activity of this series of compounds.

It could be expected that changes in the nature and position of the substituents in the phenyl radical would affect the strength and character of their central depressant effect. It became of interest to ascertain the effect of the introduction of a β-hydroxyethyl moiety into the molecule and also the effect of an increase in the distance between the phenyl moiety and the quinazolone ring (through the introduction of methylene groups between them).

The designated compounds (see Table 1) were obtained by the following methods, which have been described in the literature [1-12].



The synthesis by method 4 was accomplished as follows. To a solution of 0.11-0.12 mole of the appropriate acid chloride in 100 ml of dry benzene with agitation and cooling with ice was added dropwise a solution of 2-methyl-3-(β-hydroxyethyl)-4-quinazolone (XII) in 50 ml of dry pyridine. The reaction mixture was agitated another 15 min at ambient temperature, then heated on a water bath for 2 h, after which it was poured into water. The water layer was discarded, and the benzene layer was washed with water, dried with sodium sulfate, and the benzene was evaporated off. The residue was crystallized from a mixture of toluene and petroleum ether.

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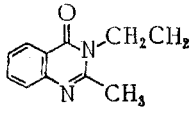
TABLE 1. Pharmacological Activity of Quinazolone Derivatives

Compound	R	mp (deg)	LD_{50} (mg/kg)	Stimulating activity				Soporific effect	Tranquilizing activity				Effect on muscle tone	Effect on experimental spasms		
				motor activity	tremor	reflex stimulation	cloric spasms		antagonism with amphetamine	fighting among mice	antagonism with morphine	hexenal sleep		corazol	electroshock	nicotine
I	—	236—237 [1,4]	500	±	++	+	+	0	0	—	++	—	±	+	0	+
II	o=$CH_3C_6H_4$	113—115[1,3,12]	500	+	+	0	0	—	—	0	—	—	±	—	—	—
III		165—168[12]	2100	0	+	0	0	0	0	—	—	—	—	—	0	—
IV	C_6H_5	146—148[1,5]	450	+	+	0	0	—	—	—	—	—	—	—	—	—
V	p=ClC_6H_4	153—155[6—8]	400	0	0	+	0	—	0	—	—	—	—	—	—	0
VI	p=$CH_3OC_6H_4$	167—169[1,7,9]	600	+	+	+	0	—	—	—	—	—	—	—	0	—
VII	p=$C_2H_5OC_6H_4$	154—156[1,7,9]	3000	0	0	0	0	—	—	—	—	—	—	—	—	—
VIII		102–104[a][7]	320	+	+	0	++	—	—	0	++	—	—	—	—	0
IX·HCl	$C_6H_5CH_2$	235—240[7,8]	230	+	+	+	+	0	—	—	++	—	++	+	—	0
X	$C_6H_5CH_2CH_2$	105—107 [1]	500	0	0	+	0	—	0	—	0	—	±	—	—	—
XI		298,5—299,5[1,11]	2500	++	++	++	0	0	—	—±		—	±	+++	0	+++
XII	—	145—147[5,10]	800	±	0	++	+	—	—	—	0	—	—	—	0	—
XIII	3,4,5=$(CH_3O)_3C_6H_2$	163—164[b]	2000	—	+	+	+	0	0	0	0	0	++	++	0	0
XIV	p=$ClC_6H_4OCH_2$	130,5—132[c]	2000	+++	0	+++	0	0	0	+++	++	—	— 0	+++	0	0
XV		154—156,5[d]	800	+	0	+	+	0	—	—	++	—	±	—	—	0
XVI		151—155[e]	800	+	0	0	+	0	0	—	0	0	±	—	0	0

[a]Found %: N 11.85. $C_{14}H_{12}N_2O_2$. Calculated %: N 11.66.
[b]Found %: N 6.90. $C_{21}H_{22}N_2O_6$. Calculated %: N 7.04.
[c]Found %: N 7.75. $C_{19}H_{17}ClN_2O_4$. Calculated %: N 7.54.
[d]Found %: N 13.60. $C_{17}H_{15}N_3O_3$. Calculated %: N 13.59.
[e]Found %: N 13.90. $C_{16}H_{15}N_3O_3$. Calculated %: N 13.59.

Denotations: +++ or --- is a strong effect; ++ or -- is a moderate effect; + or - is a weak effect; and 0 is the absence and development of an effect in toxic doses.

The known substances were characterized by their melting point and the unknown ones (compounds VIII, XIII-XVI) by elemental analysis.

The toxicity of the compounds we synthesized and their effect on the central nervous and cardiovascular systems were investigated. Experiments were carried out on white mice of the H strain weighing 18 to 24 g and on mongrel cats. The compounds were injected as suspensions (from 1 to 5%) prepared with Tween 80 intra-abdominally into the mice and intravenously into the cats. Their effect on the function of the central nervous system was investigated by the neuropharmacological screening scheme we adopted [13]; their effect on blood pressure was investigated on cats narcotized with ethyl carbamate. The substances were injected in doses from 1 to 30 mg/kg.

It is evident from Table 1 that all the quinazolone derivatives are biologically active and possess an expressed effect on the central nervous system. The strength of the central effects was calculated as the ratio between the AU and the LD_{25}. The effects (stimulating or depressing) for which the AU was less than the LD_{25} were rated as strong: when the ratios were equal or approximately equal, they were rated as moderate, and when the AU were greater than the LD_{25}, the effects were rated as weak. Their hypotensive activity was determined by the decrease in the blood pressure in percents of the original pressure.

The 4-quinazolone derivatives we investigated with respect to the nature of their central effects can be divided into three groups: 1) compounds (II-VIII, X) which possess principally a central depressant effect (tranquilizing, antispasmodic, soporific); 2) compounds (I, XI, XIII, XIV) which manifest principally a stimulating effect on the central nervous system; 3) compounds (IX · HCl, XII, XV, XVI) which possess a transient "amphoteric" effect (symptoms of excitation are combined with symptoms of depression).

An antiamphetamine effect occurs for half the compounds, among them the substances with a stimulating and "amphoteric" effect (XI, XII, and XV). Suppression of provoked agressivity (tranquilizing effect) and the ability to heighten Hexenal narcosis are still other general properties. A soporific effect, which the majority of authors feel is the basic effect of quinazolone derivatives, was noted for eight of the compounds, but it is the predominant one for only two of them.

Antispasmodic activity with respect to Corazol (11 compounds) and electroshock (eight compounds) is considerably more strongly manifested, but is most quickly manifested through the expression of a tranquilizing, central myorelaxant, and central H-cholinolytic effect. The phenomena of stimulating the central nervous system to one or another degree are noted for all the compounds except VII. They are manifested for the depressants of the first group as a mild short-lived motor stimulation, hyperreactivity and tremor, which then are replaced by soporific or tranquilizing activity. These symptoms play a leading role in the overall pattern of activity in the other two groups. The strengthening of agressiveness, the boosting of morphine activation, and clonic spasms are added to them. Muscular distonia and hypertonia with the predominance of the tonus of the extensors are manifested for the compounds with stimulating and amphoteric activity (IX · HCl, XI, XII, XV, and XVI), however, they are also detected for the substance with soporific activity (X) in the background of the lost "turnover reflex." Three compounds (IX · HCl, X, and XII) have these disruptions of muscle tone which can be considered, like symptoms of the excitation of the spinal cord, to be ended with tonic strychnine-like spasms. These phenomena are similar to the previously described "state of excitation" caused by another group of quinazolone derivatives [11].

The effect of the quinazolones we investigated on the cardio-vascular system is characterized by a weak (II, V, VI, VII, XI, XIV) to moderate (X and XII) short-lived decrease in the pressure. Preparation I constitutes an exception. With an intravenously introduced dose of 30 mg/kg, the decrease in blood pressure they bring about amounts to 80% and remains at this level for more than 120 min.

Thus, the depressant activity on the central nervous system is the prevalent one for all the compounds which contain a phenyl moiety linked to the quinazolone ring directly or through a polymethylene chain as substituents in the third position. The introduction of a methyl group in the ortho position or a methoxyl group in the para position increases the therapeutic latitude of the soporific effect by several times [14, 15, 16].

Substitution of the methoxy group in the para position by an ethoxy group leads to the loss of the soporific activity and to the appearance of tranquilizing activity, and the substitution of a hydrogen or alkoxy group by a chlorine atom increases the tranquilizing and antispasmodic properties by several times [17]. Separation of the phenyl or furyl moiety from the quinazolone heteroring by methylene groups weakens the depressive activity and strengthens the stimulation of the central nervous system. The compound which does not

contain a substituent in the third position of the ring differs from all the rest by its considerable hypotensive effect. The absence of a substituent in the third position or the presence of a methyl, ethyl, or β-hydroxyethyl group (free or esterified) brings about the presence of central stimulating properties. Esterification with p-chlorophenoxyacetic acid leads to the loss of the original convulsive activity and muscule distonia by which this group of compounds is characterized, but, at the same time, increases the other elements of the central stimulating activity.

Preparations V, VI, and VII, which are distinguished by their high therapeutic latitude, could offer the greatest interest among the substances with a depressant type of activity that were investigated in this work; this latitude provides a basis for studying them in more detail in order to examine the possibility of their practical application.

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