1-SUBSTITUTED QUINOLIN-4-ONE IMINES WITH BIOLOGICAL ACTIVITY. I

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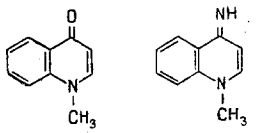
Echinopsine, 1-methylquinolin-4-one (I), was first isolated by Greshoff [1] from the seeds of species of Echinops, family Compositae, and later by Soviet authors [2] and by one of us [3]. Its valuable physiological properties (nerve-muscle stimulator) [4] have permitted the substance to be used in medicine.

In the isolation of echinopsine from plants, as an intermediate we have obtained yet another alkaloid, which we have called "echinopsidine." On saponification with caustic soda, echinopsidine is converted into echinopsine [5]. It has been shown that it is 1-methylquinolin-4-one imine (II) [6]. This product also has a pronounced biological activity, which differs from that of echinopsine.

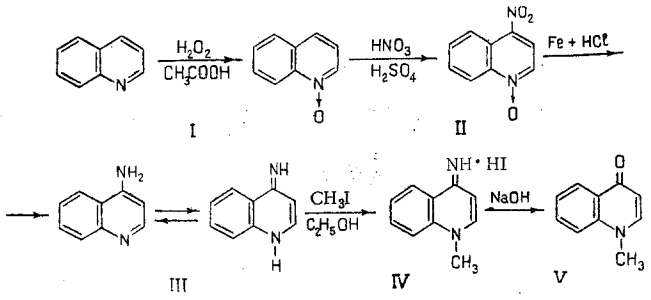


I II

Consequently, the structural difference between the two alkaloids—the different substituents in position 4 (=O or =NH group)—is responsible for the difference in their physiological effects.

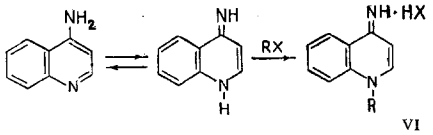
This has given us the basis for obtaining new substances with valuable therapeutic properties by synthesizing a group of quinolinone imines with the general formula VI in which R is an alkyl or aralkyl radical.

Previously [7], by making use of the relationship between echinopsidine and echinopsine we developed a four-stage method for synthesizing echinopsine from quinoline by the following route:



I II III IV V

As can be seen, echinopsidine is formed in the fourth stage. The new 1-substituted quinolinone imines (table), which may be considered as structural analogs of echinopsidine, were synthesized by the same method, but in the fourth stage the 4-aminoquinoline was treated not with a methylating agent but with various alkyl and aralkyl halides, halogen-substituted ketones, and other alkylating agents.



VI

The reaction was carried out by boiling 4-aminoquinoline with an excess of the appropriate alkylating agent in a suitable solvent. It has been established that in an alkaline medium only three compounds are obtained, namely: echinopsidine and those derivatives which contain a carbonyl group in the substituent R. In all the other cases the medium in which the reaction is carried out must be a solvent with a higher boiling point. Otherwise, depending on the

substituent R, the aminoquinoline either does not react at all or it reacts by not more than 40%, and the new product is difficult to separate from the starting material. When xylene is used as the medium (high-boiling solvent) the aminoquinoline reacts to the extent of 70–100% (for various halides) and there is no difficulty in obtaining the quinolinone imines in the chemically pure state.

R	Mp, °C	Salt	N		C		H	
			calc.	found	calc.	found	calc.	found
			%					
$-CH_3$ (echinopsidine)	229–230	Hydriodide	9.79	9.69	—	—	—	—
$-C_2H_5$	252–254	Hydrobromide	11.07	10.60	52.17	52.10	4.74	5.01
$-C_3H_7$	244–246	Hydrobromide	10.49	10.30	53.93	53.70	5.62	5.59
$-C_4H_9$	191–193	Hydrobromide	10.00	10.00	55.52	55.30	6.05	5.95
$-C_5H_{11}$	208–211	Hydrobromide	9.49	9.77	56.94	56.80	6.44	6.75
$-C_6H_{13}$	218–220	Hydrobromide	9.06	9.25	58.25	58.00	6.80	6.70
$-C_6H_5\cdot-CH_2$	285–287	Hydrochloride	10.37	10.46	71.11	71.55	5.55	5.77
$-C_6H_5\cdot-CO\cdot CH_2$	301–302	Hydrobromide	8.16	8.33	59.47	59.71	4.35	4.43
CH_3COCH_2-	282–263	Hydrobromide	10.00	10.20	51.24	51.10	4.54	4.80
$CH_2=CH\cdot CH_2-$	228–229	Hydrobromide	10.57	10.70	54.37	54.10	4.91	5.04

The time of the reaction for various compounds varied from 6 to 25 hr. The course of the reaction was monitored by thin-layer chromatography on silica gel [solvent system: ethanol–water–ammonia (70 : 80 : 1); revealing agent: modified Dragendorff's reagent].

On pharmacological evaluation, it was found that all the quinolinone imines are active with respect to the CNS, the majority of them possessing a central-stimulating and antidepressive effect.

The first member of the homologous series (R = CH_3) has the strongest antidepressive effect. With a lengthening of the carbon chain attached to the nitrogen atom to four carbon atoms, the antidepressive effect decreases and at the same time the effects of nonspecific stimulation of the CNS increase. A further lengthening of the methylene chain leads to a decrease in the stimulating effect.

The two derivatives containing an aromatic radical show elements of antidepressive activity, although it is weaker than in echinopsidine, and when a double bond is present in the substituent there is a loss of exciting effect and depression of the CNS with elements of a tranquillizing action appear.

As a second phase of the action, in large doses of the compounds myorelaxation phenomena develop. The nature and sequence of the development of the symptions shows that here there is a peripheral curare-like action. The strength of the myorelaxant effect increases if the methyl group on the nitrogen atom is replaced by a heavier radical, although there is no marked regular relationship between the size of the substituent and the strength of the effect. The benzyl derivative has a particularly strong curare-like action. Carbonyl groups in the molecule weaken the myorelaxant effect.

In doses of 0.5–3 mg/kg, the quinolinone imines cause a brief (20–30 min) lowering of the blood pressure by 30–70%. Their influence on the vegetative nervous system is characterized by the marked cholinopotentiating action of small doses; in larger doses the compounds show an atropine-like and ganglion-blocking effect.

A quantitative evaluation has shown that the addition of one or two methylene groups to the nitrogen atom leads to a manifold increase in the hypotensive and ganglion-blocking effects. When the number of methylene groups is increased to four or six, both effects fall off, and the introduction of a double bond into the substituent reduces the hypotensive activity, while the nature of the influence on the VNS is retained.

Compounds with an aromatic nucleus in the substituent are characterized by a relatively strong hypotensive and a weaker cholinolytic effect. The acetyl derivative proved to be the least active in relation to the cardiovascular system and the VNS. The potentiation of the pressor effect of norepinephrine is best expressed in the methyl, propyl, and hexyl derivatives.

A study of the anticholinesterase activity of the quinolinone imines permits the conclusion that these compounds are far more active than echinopsine, but inhibit cholinesterase more feebly than galanthamine. The first two members of the homologous series possess approximately one-tenth of the activity of galanthamine. With an increase in the number of carbon atoms in the aliphatic chain of the substituent, the activity rises, and in the hexyl derivative it

amounts to one-half of the activity of galanthamine. Compounds containing aromatic substituents show an intermediate activity, and the acetyl derivative occupies the last place in respect of this index.

Compounds containing from one to three methylene groups on the nitrogen atom have similar toxicities. The introduction of a double bond into the substituent has no effect on its toxicity. The presence of four or more carbon atoms, regardless of whether they are present in a straight or a cyclic aliphatic chain or in an aromatic ring leads to an almost twofold increase in toxicity. The existence of a carbonyl group between the nitrogen atom and the substituent markedly reduces the toxicity of the compounds.

As compared with echinopsine, the quinolinone imines are characterized by a higher biological activity and toxicity.

EXPERIMENTAL

Preparation of 1-methylquinolin-4-one imine (echinopsidine). A solution of 5 g of 4-aminoquinoline in 130 ml of ethanol was treated with 10 ml of methyl iodide, and the reaction mixture was heated at 80° C for 3 hr. The product that had deposited was recrystallized from ethanol, giving 7.2 g of substance. Yield 80%, mp 227–230° C. 1-Phenacyl- and 1-acetonylquinolin-4-one imines were obtained similarly (see table).

Preparation of 1-ethylquinolin-4-one-imine. Five grams of 4-aminoquinoline was dissolved in 150 ml of hot dry xylene, and the solution was heated at 140–150° C with stirring for 10 hr, 20 ml of ethyl bromide being added during the first 3 hr. The product that deposited was recrystallized twice from ethanol, giving 6.8 g of substance. Yield 75%, mp 252–254° C.

The other compounds were isolated similarly (see table).

CONCLUSIONS

The interrelationship between structure and pharmacological activity has been studied in a series of 1-substituted quinolin-4-one imines. It has been shown that some derivatives may be of interest for medicinal use.

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