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TOXIC AND ANTIMITOTIC PROPERTIES OF A SERIES OF COLCHICINE DERIVATIVES

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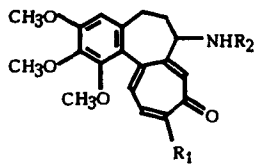
Colchicine and its natural analog colchamine possess pronounced stathmokinetic properties, but only colchamine, which has a lower toxicity but a narrow breadth of therapeutic action, is used in oncology. Our task was to find substances with lower toxicity and retained mitosis-inhibiting activity among new analogs of these alkaloids.

It is known that the introduction of amino compounds into the tropolone ring of colchicine (**1**) and colchamine (**9**) leads to a lowering of toxicity. We obtained the following derivatives: amino- (**2**), monoethanolamino- (**3**), mercaptoethylamino- (**5**), diethylamino- (**6**), chloroethylamino- (**7**), and dichloroethylaminocolchicine (**8**) and monoethanolaminocolchicine derivatives (**10**). The acute toxicities and mitotic indices (MIs) of these substances were determined on crypts of the intestines of mice of the $C_{57}Bl/6$ line. Acute toxicities were determined by the intraperitoneal (i/p) administration of the substances under study to mice weighing 20-22 g, and MIs also by the i/p administration of the preparations in doses corresponding to 1/2 LD_{16}.

Animals were decapitated after 30 and 60 min and each hour in the course of a day, and 1 cm of the duodenum (taken 1 cm below the pyloric end of the stomach) was used for histological investigations. This section of the duodenum was fixed in Bowen's mixture and was then flooded with paraffin, and histological sections were prepared and were stained with hematoxylin–eosin. Under the microscope, the number of cells in a crypt and the number of dividing cells were counted, and the MI and mitotic activity were calculated. On average, not less than three animals were used for each point.

As can be seen from Table 1, replacement of the methoxy group of the tropolone ring by various amino compounds lowered the toxicity by a factor of more than 10. The formation of hydrochlorides (**4**, **6**) increased water solubility but doubled toxicity. An increase in the number of ethanolamine groups had practically no effect on the toxic properties. The chloroethyl-

TABLE 1



Compound No.	Toxicities and mitotic indices of the compounds investigated		Literature	Toxicity, mg/kg			MI, time of investigation, h (M±m)		
	R_1	R_2		LD_{16}	LD_{50}	LD_{84}	1	3	6
1	$-OCH_3$	$-COCH_3$		2.7	3.9	5.1	10.3±0.3	21.8±0.3	35.7±0.3
2	$-NH_2$	"			100		12.2±0.2	22.1±0.5	21.1±0.4
3	$-NH-CH_2-CH_2-OH$	"	[1]	52	82	130	13.6±0.2	27.4±0.7	22.3±0.6
4	$NH-CH_2-CH_2-OH \cdot HCl$	"	[2]	24	37	56	12.1±0.1	17.2±0.4	18.9±0.1
5	$-NH-CH_2-CH_2-SH$	"	[1]		50		5.9±0.1	5.9±0.1	4.7±0.1
6	$-N(-CH_2-CH_2-OH)_2 \cdot HCl$	"	[2]	31	35	40	11.1±0.1	11.6±0.1	23.2±0.2
7	$-NH-CH_2-CH_2-Cl \cdot HCl$	"	[3]	34	50	72	11.7±0.2	23.1±0.7	16.9±0.3
8	$-N(-CH_2-CH_2-Cl)_2 \cdot HCl$	"	[4]		40		11.1±0.1	26.5±0.3	25.2±0.9
9	$-OCH_3$	$-CH_3$		38	56	73	10.0±0.2	19.9±0.4	31.6±0.6
10	$-NH-CH_2-CH_2-OH$	"	[5]	135	175	225	13.7±0.1	19.6±0.4	7.2±0.1
Control							5.5±0.1	5.7±0.3	6.3±0.3

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amine derivatives (**7** and **8**) had somewhat lower toxicities than the ethanolamine derivatives (**4** and **6**) but the substances had lost their solubility in water.

Only an hour after the administration to the animals, the mitotic indices of the compounds had increased in comparison with the control and had increased slightly in comparison with the initial alkaloids. Subsequently, for the derivatives the number of mitoses either rose for 6 h (**4** and **6**) or they reached maximum values after 3 h (**2**, **3**, **7**, **8**, and **10**) and fell by the 6th hour. An exception was the mercaptoethanolamine derivative (**5**), on the administration of which the MI of the epithelium of an intestinal crypt did not change. After 3 h, substances (**2**, **3**, **7**, and **8**) caused a more powerful stathmokinetic action than colchicine and colchamine, the maximum effect of which was shown after 6 h, when the MIs of these derivatives had fallen somewhat. However, a comparison of the antitumoral actions of compounds (**7** and **8**) with those of the initial alkaloids showed that (**7** and **8**) possessed a more pronounced capacity for inhibiting the growth of transplantable strains of Walker's carcinoma and sarcoma-45 (by 55-62%; colchicine by 46 and 33%, respectively). Consequently, the earlier increase in the mitotic index (in the first 1-3 h) is responsible for their better chemotherapeutic action.

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