RELATIONSHIP OF STRUCTURE AND ACTIVITY IN THE COLCHICINE SERIES

V. V. Kiselev

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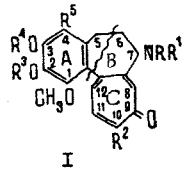
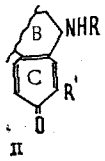
The antimitotic activity of colchicine (1), i.e., its capacity for inhibiting the division of the cell nucleus, has been studied since the middle thirties [1]. The possibility of treating malignant neoplasms with colchicine was shown at that time [2]. However, the considerable toxicity of this drug was an obstacle to its use [3]. Among colchicine compounds, only an alkaloid of plants of the genus *Colchicum*, colchamine (2), has acquired limited value [4, 5].

Numerous reviews have been devoted to the chemical properties of colchicine and its structure and synthesis [6]. The structure of colchicine (1) (formula I) shows its multiple reactivity. For example, the methoxy group in position 10 of ring C readily undergoes hydrolysis. The colchiceine (3) obtained gives, on methylation, a mixture of colchicine and its isomer isocolchicine (4) (formula II); the introduction of other alkyl groups gives derivatives of both (1) and (4). The methoxy group mentioned can be replaced fairly readily by, for example, various amino groups. In ring B, variation is possible at the acetylamino group in position 7. In ring A, changes can be brought about by the appearance of hydroxyls at C-2 and C-3 and of substituting groups at C-4.



I

Colchicine 1:
$R = H$; $R^1 = COCH_3$
$R^2 = OCH_3$; $R^3 = R^4 = CH_3$
$R_5 = H$



II

Isocolchicine 4:
$R = COCH_3$
$R^1 = OCH_3$

Much information has been published on the activity of the substances considered, but the elucidation of the structure–activity relationships is hampered by the heterogeneity of the available facts. Their antimitotic action has been determined: *in vivo* – in regenerating rat liver [7, 8, 9], in rat bone marrow [10], on the corneal epithelium of the mouse [4, 11, 12] and of the rat [11, 13], on mouse spermatogonia [14], and on the ascitic form of a tumor [15, 17, 18]; and *in vitro* – on fibroblasts [18-26], on a culture of the tissue of a transplanted mouse mammary gland tumor [27], on leucocytes [22, 28], and on the isolated mitotic apparatus of sea urchin eggs [29]. Antitumoral activity has been established: on primary tumors of a) the mouse – adenocarcinoma of the mammary gland [4, 11], sarcoma 180 [30], sarcoma 37 [31-33], sarcomas AK and M-49 [34], Ehrlich's carcinoma, and leukemia L 1210 *in vitro* [35, 36] and *in vivo* [25, 26, 37], and b) of the rat – sarcomas M-1 [4, 11, 34], 45 and 536 [34], Walker's carcinosarcoma 256 [16, 38], and the Flexner–Jablin carcinoma [38]. Investigations have been made of their inhibition of the growth of the meristem of the roots of *Allium* [39], of their interaction with tubulin – the protein of the microtubules* [41-44], of their antiinflammatory action [41, 45-47], and of their capacity for interrupting pregnancy in mice and rabbits [48] and for inhibiting the activity of the thyroid gland [49]. For derivatives containing an OPO_3Na_2 group the sensitivity to the action of the acid phosphatase of the prostate has been determined [28]. Their toxicity has been determined in mice [10, 23, 25, 26, 28-34, 37] and in rats [7-9, 34]. The nature of the toxicity changes

*Microtubules are organelles (parts of cells), in particular, consisting of the fibrous framework of the mitotic spindle, and they are associated with various functions inherent in the cell [40]. The tubules are considered as a receptor of poisons of the spindle, which include colchicine.

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to a greater or smaller extent in comparison with colchicine when there is a hydroxy, amino, or thio group at C-10 in place of the methoxyl. The figures for the biological activities of the compounds discussed are given in Table 1.

For many substances with a strong antimitotic action and with a low toxicity, no results of investigations of antitumoral action in animals have been published [34]. Apparently, even for already known compounds related to colchicine the question of antitumoral activity has not been exhausted. The possibility of obtaining new substances of this series with more favorable ratios of antitumoral activity and toxicity has been reported [9, 30, 31, 50, 51]. However, the existence of activity has been shown only for toxic compounds [9].

Colchicine compounds with acidic, basic, and neutral properties are known. The combination in one compound of acidic and basic substituent groups yields amphoteric substances. The generalization has been made that amphoteric compounds possess no antimitotic activity; such a compound is deacetylcolchiceine (5) [19]. The neutral colchicine is highly active, while a substance with acidic properties, colchiceine (3) possesses activity, although it is 450 times weaker, and the activity of the base deacetylcolchicine (6) is close to that of colchicine (1). For (6), the difference between the effective and toxic doses is considerably greater than for (1) [30, 31]. Consequently, the most favorable result is obtained for a substance of basic nature. The amino group of aminocolchicide (colchiceinamide) (7) possesses somewhat different properties from that in (6): it is close to the amino groups of carboxylic acid amides. The antimitotic action of substance (7) is close to that of (1), but it is less toxic. Methylaminocolchicide (8), ethylaminocolchicide (9), and dimethylaminocolchicide (10) are similar to substance (7). With relation to the toxicity of colchamine (2), the opinion has been expressed [4] that there are considerable differences in the published figures. However, on careful reconsideration the references to the literature given on this question [4] disprove this idea. For some aminodeacetyl-N-methylcolchicides obtained from colchamine (2) [52], retention of activity in a culture of tumor tissue with a considerably lower toxicity has been shown [2, 23]. Furthermore, the more favorable properties of the basic substances (6-10) and some others have been shown in *in vivo* experiments [32]. The results of investigations on transplanted tumors of the bases (2), (6), and (7) and N-methylcolchamine (11) are similar [34].

TABLE 1. Structures of the Compounds and Information on Their Activity[1)]

Substance	Structure[2)]	Biological activity		Literature
		figures expressing the activity[3)]	toxicity, mg/kg	
1	I	0,01–0,03 μg/ml[4)]		19,21
		1,5[5)]	3[13)]	31,32
		0,02[6)]	0,5[14)]	7
		2[6)]	LD_{100} 5[14)]	9
		0,7[7)]	LD_{50} 2±0,3[13)]	10
		0,5[8)]	2,5[14)]	34
			3,1[13)]	34
		87,7%[9)]		41
		$2,5\times10^{-7}$ mole/ml [10)]		39
		$1,5\times10^{-7}$ mole/ml [10)]		76
2	II. $R^1=CH_3$	5[6)]	LD_{100} 35	9
		1,5[8)]	29[14)]	34
			56,0[13)]	34
		87,86%[9)]		41
		60,2%[11)]		41
3	I. $R^2=OH$ or II. $R^1=OH$	4,5 μg/ml [4)]		19
		75[5)]	150[13)]	31
		0,8[6)]	3,0[14)]	7
		>100[6)]	LD_{100} >100[14)]	9
		1,2[8)]	2,5[14)]	34
			22,0[13)]	34
		25%[9)]		41
		6,6±1,2%[11)]		41
		$10^{-5.2}$ M[4)]		27

TABLE 1 (Continued)

Substance	Structure[2]	Biological activity		Literature
		figures expressing the activity[3]	toxicity, mg/kg	
4	II		200[13]	33
		>200[6]	LD_{100} >400[14]	9
		2,1±2,2%[11]		41
		(7%)[9]		41
		140×10^{-7}M[10]		76
5	I. R^1=H, R^2=OH or	>100 μg/ml [4]		19,21
	II. R=H, R^1=OH	600[5]	600[13]	31
		7,2[8]	23[14]	34
			130[13]	34
		0,8±1,5%[11]		41
		(26%)[9]		41
6	I. R^1=H tartrate	0,05 μg/ml [4]		19,21
		2[5]	100[13]	32
		2[7]	LD_{50} 20±4[13]	10
			LD_{100} 30[14]	9
		1,4[8]	20,0[14]	34
			35,0[13]	34
		52,9±0,9%[11]		41
		78.86%[9]		41
		$12,5\times10^{-7}$ mole/ml		39
7	I. R^2=NH_2	0,01 μg/ml[4]		18,21
		2[5]	40[13]	32
		8[6]	LD_{100}30[14]	9
		1,6[7]	LD_{50}52±14[13]	10
		1,5[8]	29,6[14]	34
			43,0[13]	34
		82,1±0,51%[11]		41
		78,75%[9]		41
8	I. R^2=$NHCH_3$	0,0025 μg/ml[4]		19,21
		1[5]	3[13]	32
			LD_{100} 3[14]	9
		0,4[8]	2,0[14]	34
			4,5[13]	34
		$1,5\times10^{-7}$mole/ml[10]		39
9	I. R^2=NHC_2H_5	0,03μg/ml[4]		19,21
		2[5]	6[13]	32
10	I. R^2=$N(CH_3)_2$	0,005 μg/ml[4]		19,21
		2[5]	5[13]	32
		2[6]	LD_{100} 20[14]	9
11	I. R=R^1=CH_3	0,005 μg/ml[4]		19,21
		2[5]	5[13]	32
		2[6]	LD_{100} 20[14]	9
12	I. R^2=NHC_3H_7	0,08 μg/ml[4]		19,21
13	I. R^2=NHC_4H_9	0,09 μg/ml[4]		19,21
		30[5]	100[13]	32
14	I. R^2=$NCH_3C_3H_7$	0,5 μg/ml[4]	LD_{100}40[14]	9
				19,21
15	I. R^2=$N(C_2H_5)_2$	5[5]	10[13]	32
16	I. R^2=$N(CH_2CH_2OH)_2$	10[5]	40[13]	32
17	I. R^1=H, R^2=NH_2	90,0[8]	320,0[14]	34
			253,0[13]	34
18	I. R^1=CH_3, R^2=NH_2	1 μg/ml[4]		22
19	I. R^1=CH_3, R^2=OH	6,0[6]	LD_{100}>100[14]	9
			50,0[14]	34
			100,0[13]	34
20	I. R=CH_3	2[6]	LD_{100} 5[14]	9
		0,5[8]	3,4[14]	34
			2,9[13]	34
21	I. R^1=CHO		LD_{100}>100[14]	9
		0,5[8]	4,4[14]	34
			9,2[13]	34

TABLE 1 (Continued)

Substance	Structure[2]	Biological activity: figures expressing the activity[3]	Biological activity: toxicity, mg/kg	Literature
22	I. $R=CH_3$, $R^1=COC_2H_5$	2[6]	LD_{100} 7[14]	9
23	I. $R^1=COC_6H_5$	40[5]	80[13]	31
			$LD_{100}10$[14]	9
24	I. $R^1=COC_2H_5$	0,006 μg/ml[4]		19,21
			$LD_{100}10$[14]	9
25	I. $R^1=COC_5H_{11}$	0,06 μg/ml[4]		19,21
26	I. $R_1=COC_3H_7$	0,001 μg/ml[4]		19,21
27	I. $R^1=COCH_2Cl$	0, 01μg/ml[4]		20,21
28	I. $R^1=COCH_2Br$	0,05 μg/ml[4]		20,21
29	I. $R^1=COCH_2J$	0,08 μg/ml[4]		20,21
30	I. $R^1=COCH_2F$	0,003 μg/ml[4]		20,21
31	I. H in place of NRR^1	0,002 μg/ml[4]		19,21
		$0,01\times10^{-7}$ mole/ml[10]		39
		$10^{-5.7}$ M[4]		27
32	I. H in place of NRR^1, $R^2=OH$	$10^{-5.45}$ M[4]		27
33	I. $R^2=SCH_3$	0,002 μg/ml[4]		20
		1[7]	$LD_{50}1\pm0,19$[13]	10
		$1,5\times10^{-7}$mole/ml[10]		39
34	I. $R^1=H$, $R^2=SCH_3$	10^{7}	$LD_{50}210\pm12$[13]	10
		50,43%[9]		41
		67,1±1,7%[11]		41
		$1,5\times10^{-7}$mole/ml[10]		39
35	I. $R^2=SCH_3$, $R^4=H$	1,3[7]	$LD_{50}30\pm7$[13]	10
36	I. $R^1=R^4=H$, $R^2=SCH_3$	>100[7]	$LD_{50}500\pm25$[13]	10
37	I. $R^2=SCH_3$, $R^4=C_6H_{11}O_5$	>30[7]	$LD_{50}22,5\pm1,2$[13]	10
38	I. $R^4=C_6H_{11}O_5$	>100[6]	$LD_{100}200$[14]	9
		>400[7]	$LD_{50}280\pm52$[13]	10
		3,2±1,2[11]		41
		(2%)[9]		41
		250×10^{-7}mole/ml [10]		39
39	I. $R^1=COCH_2Cl$, $R^2=SCH_3$	0,004 μg/ml[4]		20,21
40	I. $R^1=COCH_2F$, $R^2=SCH_3$	0,001 μg/ml[4]		20,21
41	I. $R^1=COC_6H_2(OCH_3)_3$ $R^2=SCH_3$	5 mg 200%[12]	$LD_{50}58,5$[13]	25
42	I. $R^1=CSNHC_3H_5$, $R^2=SCH_3$	1,148%[12]	$LD_{50}150$[13]	26
43	I. $R^1=COCH_2CH_2COOH$, $R^2=SCH_3$	15,325%[12]	$LD_{50}216\pm11,6$[13]	37
44	I. $R^1=H$, $R^2=SC_2H_5$	>100[7]	$LD_{50}265\pm25$[13]	10
45	I. $R^1=CH_3$, $R^2=SCH_3$	4[7]	$LD_{50}15\pm5$[13]	10
46	I. $R^2=NH_2$, $R^3=C_6H_{11}O_5$	>400[7]	$LD_{50}365\pm49$[13]	10
47	I. $R^4=H$	5[6]	$LD_{100}25$[14]	9
		5,7[7]	$LD_{50}16\pm2,5$[13]	10
		$12,5\times10^{-7}$mole/ml[10]		39
48	I. $R^3=H$	15[6]	$LD_{100}70$[14]	9
49	I. $R^2=NH_2$, $R^4=H$	8[7]	$LD_{50}80\pm17$[13]	10
50	I. $R^2=NHCH_3$, $R^4=H$	0,6[7]	$LD_{50}2,4\pm0,6$[13]	10
51	I. $R^2=N(CH_3)_2$, $R^4=H$	2,3[7]	$LD_{50}27\pm7$[13]	10
52	I. $R^2=C_2H_5$	2–3[6]	LD_{100} 5[14]	9
53	I. $R^4=COCH_3$	4[6]	$LD_{100}10$[14]	9
54	I. $R^3=C_2H_5$	1,5[6]	LD_{100} 4[14]	9
55	I. $R^3=C_3H_7$	1[6]	LD_{100} 2[14]	9
56	I. $R^3=COCH_3$	30[6]	$LD_{100}30$[14]	9
57	I. $R^5=CN$	2–2,5[7]	$LD_{50}130$[13]	66
58	I. $R^5=CH_3$	1,1[7]	$LD_{50}35$[13]	68

TABLE 1 (Continued)

Substance	Structure[2]	Biological activity: figures expressing the activity[3]	Biological activity: toxicity, mg/kg	Literature
59	I. R^2=$NHCH_3$, R^5=CN	0,6[7]	LD_{50}50[13]	70
60	I. R^4=H, R^5=$CHCH{=}CH_2$	0,6[7]	LD_{50} 5[13]	70
61	I. R^2=$NHCH_3$, R^5=CH_3	0,8[7]	LD_{50}15[13]	69
62	I. R^2=SCH_3, R^5=CN	0,9[7]	LD_{50}40[13]	66
63	I. R^2=SCH_3, R^5=CH_3	1,6[7]	LD_{50}60[13]	68
64	I. R^5=CH_2OH	12[7]	LD_{50}670[13]	73
		500×10^{-7} mole/ml[8]		39
65	I. R^5=CH=NOH	7,5[7]	LD_{50}300[13]	65
66	I. R^2=SCH_3, R^5=CH_2OH	9,5[7]	LD_{50}300[13]	67
67	I. R^2=SCH_3, R^5=CHNOH	4,7[7]	LD_{50}75[13]	65
68	I. R^2=$NHCH_3$, R^5=CH_2OH	4[7]	LD_{50}200[13]	75
69	II. R=H	(16%)[9]		41
		4,4±1,2%[11]		41
			1500[13]	33
70	I. R^2=H			29
71	III	0,1μg/ml[4]		19
		122[5]	500[13]	32
		6,8±1,1%[11]		41
		28%[9]		41,45
72	III. R=COOH		>1000[13]	33
			LD_{100}>100[14]	9
		3,7±2,4[11]		41
		(0%)[9]		41,45

[1]The figures given do not exhaust the factual material from the cited literature. Furthermore, additional information is given in [82].

[2]The information given consists of the structural formulas (Roman numerals) and the radicals by which the compounds differ from colchicine (1), isocolchicine (4), or colchinol (71).

[3]Dose in mg/kg, concentration, inhibition, etc.

[4]Inhibition of mitosis *in vitro*.

[5]Sarcoma 37 (mouse).

[6]Inhibition of mitosis *in vivo*, regenerating liver (rat).

[7]Inhibition of mitosis *in vivo*, bone marrow (rat); dose at which 100 mitoses per 100 cells are observed.

[8]Sarcoma 45 (rat).

[9]Inhibition of experimental edema at a dose of 2 mg/kg in percentage of the control; insufficiently reliable results are given in parentheses.

[10]Allium test.

[11]Inhibition of the binding of [^{3}H] colchicine by tubulin in percentages at a concentration of the compound tested of $2.5\cdot10^{-5}$ M.

[12]Leucosis L 1210 (mouse); the daily doses for 12 days and the survival time in comparison with the control are given. Individual animals died.

[13]Mice.

[14]Rats.

The advantages of the bases of the colchicine series have been mentioned in several papers [34, 53-55], but there is no absolute rule. For example, an increase in the size of the radical in an amino group introduced into position 10 (formula I) has an adverse influence: N-propylaminocolchicide (12), N-butylaminocolchicide (13) and some others are less active than 1 [19, 21, 22, 32, 51]. Also less active than colchicine (1) are disubstituted derivatives: methylpropylaminocolchicide (14), diethylaminocolchicide (15), and di(β-hydroxyethyl)aminocolchicide (16) [32]. Another limitation is that when a second unacylated amino group is present there is frequently no improvement in the antitumoral activity of the substance. Thus, it has been found that aminodeacetylcolchicide (17) [23] is inferior not only to aminocolchicide (7) but also to (1) [34]. Amino-N-methyldeacetylcolchicide (18), which is the amide of colchamine (19), is similar [22]. The same thing has been observed for other aminodeacetylcolchicides [16]. For six dialkylaminoethylaminocolchicides the antimitotic action has been compared with the dissociation constants: no relation was found [56]. It is possible that the dissociation constants here are in too narrow a range to show any regularity. The ratio of activity and toxicity for colchamine (2) worsens on acetylation [9, 34], and N-acetylcolchamine (20) is practically equivalent to (1). Other of its N-acylated analogs also approximate to colchicine. This applies to formyldeacetylcolchicine (21) and propionylcolchamine (22) [9, 34]. Benzoyldeacetylcolchicine (23) is closer to (1) than to (6) [9, 30, 31]. In relation to their antimitotic action *in vitro*, propionyl- and caproyldeacetylcolchicines (24 and 25) are close to (1), and butyryldeacetylcolchicine (26) is superior to it. A special position is occuplied by the halogenocolchicines [27-30] [57] with antimitotic actions similar to or greater than that of colchicine. Chlorocolchicine (27) has been used in clinical medicine in the form of an ointment for the treatment of basalioma [20, 58].

Deacetamidocolchicine (31) has been obtained by complete synthesis [59, 60], and also from colchicine itself [59]. Its antimitotic action is greater than that of (1) [21, 61]. In a number of cases, its activity is higher than that of (1) by a factor of 5-10 [27, 38, 39, 62]. Compound (31) has shown a low activity against experimental edema [47].

Both in antitumoral activity and in relation to other types of biological activity colchiceine (3) is less effective than (1): a decrease in its action on the protein of the microtubules [41] and of its inhibition of experimental edema [41, 45] and of the secretion of the thyroid gland [46] has been observed. The analogs of (3) also have only a low activity. This applied to deacetylcolchiceine (5) [19, 21, 30, 31].* Deacetamidocolchiceine (32) has a ∿1000 times weaker *in vitro* action that (31) [27]. An alkyl group attached to the oxygen atom in ring C at C-10 has been recognized as a necessary condition for the substance to be fairly active [31]. A sharp fall in activity on the hydrolysis of the labile methoxy group has also been reported by other workers [19, 24].

It can be seen from the cases of thiocolchicine (33) [10, 20, 39, 63] and deacetylthiocolchicine (34) [10, 39, 41, 45], 3-demethylthiocolchicine (35) [10], and 3-demethyldeacetylthiocolchicine (36) [10] that thio derivatives retain their biological activity with a substantial reduction in toxicity. However, for thiocolchicoside (37), obtained from colchicoside (38) no antimitotic properties have been detected, and its toxicity is greater [10] and it shows an increase in central activity [64]. Apparently, an antimitotic action is retained in those thio derivatives of colchicine for which the original substance possessed such action. Also in agreement with this conclusion are the high antimitotic activities of (33), chlorothiocolchicine (39), and fluorothiocolchicine (40) [57]. The last-mentioned compound is the first of the colchicine series having an antimitotic activity greater than that of vincaleucoblastine, the active concentration of which is 0.002 μg/ml [20, 21]. An increase in the basicity of the thio derivatives also has a positive effect on the chemotherapeutic properties, as can be seen by comparing (33) and (34). However, N-acylation with certain acyls gives substances (41-43) (see Table 1), the properties of which are apparently not inferior to those of (34) [25, 26, 37]. This, like the properties of the halogenothiocolchicines mentioned above, shows that it is not any kind of acylation of the amino group in the colchicine series that leads to a worsening of the properties. In a number of cases, the toxicity of the thio derivatives is considerably reduced [10, 65-68], and its nature is different. This applies to thiocolchicoside (37) and also to 3-demethyldeacetylthiocolchicine (36). Some difference from colchicine in the nature of their toxicity is characteristic for (34), (35), S-ethyldeacetylthiocolchiceine (44), and methyldeace-

*However, this substance has been recommended as an agent for combatting gout. In this case the mechanism of its action is apparently different from that of colchicine [47].

tylthiocolchicine (45). In the nature of its toxicity, thiocolchicoside (37) is similar to colchicosamide (46) [10].

The natural alkaloids of *Colchicum* C (47) and E_1 (48) are examples of changes in the substituents of ring A. The ratio of activity and toxicity for each of them is more favorable than for (1). In the ratio of activity to toxicity [9, 10], amino-3-demethylcolchicide (49) and the compound from which it was derived (47), are similar to (1) and (7) [19, 21, 32]. An analogy is also observed on passing from (47) to methylamino- and dimethylamino-3-demethylcolchicides (50 and 51). These results contradict the views mentioned above [19] concerning the adverse influence of amphotericity. The nature of the group imparting acidity apparently has an influence.

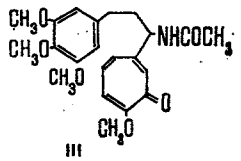
With respect to the ratio of activity and toxicity, the O-ethyl and O-acetyl derivatives (52 and 53) are similar to colchicine (1). A natural O-glucosyl compound — colchicoside (38) — is practically free from antitumoral activity [9, 10], and its toxicity is considerably lower than that of (1) [10]. The O-ethyl and O-propyl ethers (54 and 55) of the alkaloid E_1 (48) are closer to (1) than to (48), as is observed for (52) [9]. The acetylation of (48) leads to substance (56) with an effective dose equal to the toxic dose [9].

Many colchicine derivatives containing a substituting group in position 4 have been obtained synthetically. A general feature for the compounds with such a group that have been investigated experimentally is their low toxicity with the retention of antimitotic activity. In a number of cases, the latter approaches that of colchicine: 4-cyanocolchicine (57) [66], 4-methylcolchicine (58) [68], 4-cyano-10-methylaminocolchicide (59) [70], 4-allyl-3-demethylcolchicine (60) [71], 4-methyl-10-methylaminocolchicide (61) [68], 4-cyanothiocolchicine (62) [66], and 4-methylthiocolchicine (63) [68]. The least active compounds with substituents in position 4 are those containing chlorine or oxygen atoms [65, 67, 69, 72, 73]. Substances without electron-acceptors in the substituent are more active. On passing from 4-hydroxymethylcolchicine (64) and the oxime of 4-formylcolchicine (65) to 4-hydroxymethylthiocolchicine (66) and the oxime of 4-formylthiocolchicine (67) the toxicity and activity rise with a decrease in the absolute and relative differences between them [65, 67, 73]. There are similar changes in the case of a 4-CN group — compounds (57) and (62). These relationships contradict the fall in toxicity mentioned above for thio derivatives. In the case of 4-methylated compounds, however, on passing from (58) to (63) there is some fall in toxicity and activity. Comparisons between 4-substituted derivatives in relation to compounds of the type of aminocolchicide (7) are possible only for a small number of examples: these are the pairs (64)—4-hydroxymethyl-10-methylaminocolchicide (68) and (57)—(59). As for other transitions to amines, here the activity rises [70, 73, 74, 75].

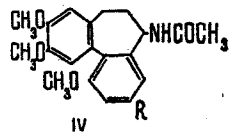
Numerous investigations have demonstrated the considerable, almost complete, loss of biological activity of colchicine (1) with the rearrangement of the functional groups of ring C. For example, the *Allium* test showed that isocolchicine (4) is approximately 90 times weaker than (1) [76]. Similar results have been obtained by other methods. In the case of analogs of (4), again the activity fell: deacetylcolchicine (6) inhibited mitosis more strongly than the isomer (69) by a factor of about 4000 [24]. The activity of (69) is low with other methods of determination, as well [24, 41, 45]. Isomers of deacetamidocolchicine (31) [27], aminocolchicine (7) [41, 45], and deacetylthiocolchicine (34) [10] are also only feebly active.

The weakening of the effect on demethylation in the tropone ring (ring C) — for example, in (3), (5), and (19) is explained not only by the change in the oxygen function but also, apparently, by the existence of an iso structure [32, 33]. However, judging from the magnitude of the specific rotation of (5), the existence of this substance only in the iso form is doubtful [33]. Isocolchicine (3) feebly inhibits mitosis in metaphase, which is ascribed to the stabilization of the proton of the hydroxyl (formula II, R = H) by a hydrogen bond with the carbonyl of the acetyl group [27]. The elimination of the carbonyl or its presence in a different position in ring C also leads to a substantial lowering of the activity [27]. Without the methoxyl of ring C, e.g., in colchicide (70), the antimitotic effect is retained with a considerable reduction in toxicity [29].

The dextro-rotating isomer of colchicine has been obtained synthetically [77]. It inhibits mitosis *in vitro* 100 times more feebly than (—)-colchicine (1) [21, 61]. This shows the influence of steric factors on activity [61]. For other compounds such an effect had been observed previously [78]. The compound with formula III differs from colchicine by the



III



IV

Colchinol 71:
R = OH

absence of a C–C bond between rings A and C. This substance shows no antimitotic action, which must be explained by the spatial instability of the mutual positions of the rings mentioned [61]. The spatial structure of compounds of the colchicine series apparently explains the puzzlingly high activity of deacetamidocolchicine (31). In this substance the center of asymmetry present in colchicine at C-7 has been eliminated and it should have no biological activity. However, for (31) obtained from natural colchicine optical activity has been detected in the ultraviolet part of the spectrum [61], which is obviously due to a fixed asymmetric spatial structure of the molecule, which apparently also exists in natural colchicine [61]. In relation to the asymmetric C-7 carbon atom of colchicine, it has been suggested that spatially it does not correspond to a receptor. Consequently, interaction with the latter is facilitated when the asymmetry at C-7 is eliminated, and the activity rises [61].

The phenomenon of the mutarotation of isocolchicine (4) is known; it is due not only to the asymmetry of the molecule at the C-7 carbon atom but also to the mutual positions of rings A and C in space [79]. We assume that, as in other cases of mutarotation, here there is a steric instability which may also be the cause for the low biological activity in the isocolchicine series. In substances with the substituents in ring C in the same position as in colchicine, no mutarotation is observed, which shows stability of the spatial structure.

The tropone ring of colchicine compounds can be converted into a benzene ring. The colchinol (71) and some of its derivatives obtained in this way are less active than colchicine (1). Another product of benzoidation — colchicinic acid (72) — is inactive [7, 9, 12, 19, 30, 31, 41, 45, 49].

In broad outlines, an agreement of the antimitotic and antitumoral activity with inhibition of the inflammatory process and of the activity of the thyroid gland, and also with affinity for the protein of the microtubules, has been established in the colchicine series. Consequently, the conclusion has been drawn that the biological action of colchicine compounds is based on their interaction with the protein of the microtubules [41]. This view of the mechanism of the inhibition of mitosis has become generally accepted [41, 45, 46, 49, 80, 81].

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SOME FEATURES OF THE GLYCOSYLATION OF POLYCYCLIC ALCOHOLS WITH CARBOHYDRATE 1,2-ORTHOESTERS

N. I. Uvarova, G. I. Oshitok, A. M. Tolkach, and G. B. Elyakov

UDC 547.455+547.918+547.922

The majority of synthetic glycosides of triterpenoids and steroids has been obtained by the Koenigs–Knorr method or its various modifications [1, 2]. At the present time, the orthoester method has come to be used successfully for this purpose [3-7]; it is characterized by a high stereospecificity and a good reproducibility of the results. A complicating factor in the synthesis of glycosides of polycyclic alcohols by the orthoester method has been the formation of byproducts — ethers and acetates of the initial alcohols [7]. The isolation of these compounds permits us to consider the final result as the sum of three processes: glycosylation, transesterification, and the subsequent conversions of the transesterification products (Schemes 1 and 2).

The simultaneous occurrence of glycosylation and transesterification can be explained by the dual reactivity of carbohydrate orthoesters [3, 5, 8]. Since in the glycosylation with α-D-maltose (methyl orthoacetate) (I) and with α-D-glucose 1,2-(tert-butyl orthoacetate) (II) of cholesterol, β-sitosterol, 16-dehydropregnenolone, and betulin and its mono-

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