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TOXICITY AND LOCAL ANESTHETIC ACTIVITY OF DITERPENOID ALKALOIDS

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The toxicity and local anesthetic activity of 74 diterpenoid alkaloids differing in the nature and position of functional groups in lycoctonine, heteratisine, napelline, hetisane, atisane, and denudatine skeletons and their synthetic derivatives were investigated. Compounds with local anesthetic activity and duration of action surpassing that of cocaine for surface anesthesia and that of novocaine and lidocaine for infiltration and trunk administration were identified. Structural factors affecting the toxicity and local anesthetic activity of the studied compounds were discussed.

Key words: diterpenoid alkaloids, *Aconitum*, *Delphinium*, toxicity, local anesthetic activity, structure—activity.

Preparations from plants of the genera *Aconitum* and *Delphinium* have for a long time been used in traditional medicine of several countries as analgesic agents [1-3].

Research has found that separate total preparations and individual diterpenoid alkaloids (DA) from *Aconitum* and *Delphinium* exhibit high analgesic activity. The alkaloids aconitine, mesaconitine, lappaconitine, and *N*-deacetyllappaconitine have higher analgesic activity than indomethacine and morphine [4-9]. The analgesic activity of these compounds is not mediated through opioid receptors.

We have previously shown that DA exhibit high antiarrhythmic activity. The mechanism of their antiarrhythmic activity is based on suppression of transmembrane sodium currents [10-12].

This research resulted in the incorporation into medical practice of the antiarrhythmic preparations allapinine (lappaconitine hydrobromide) and aclesin (total alkaloids from *A. leucostomum*). The antiarrhythmic properties of DA and their ability to suppress sodium currents of excited membranes suggest that they have local anesthetic activity.

Herein we review research on the search for local anesthetics among DA and their derivatives of various structural types that were isolated from plants of the genera *Aconitum* and *Delphinium* and examine the structure—toxicity relationships of the studied compounds.

A total of 74 DA and their derivatives with various heterocyclic structures containing a tertiary *N* atom and the nature and location of the functional groups were studied. The compounds can be divided according to the structure of the carbon skeleton into alkaloids with the lycoctonine, heteratisine, napelline, denudatine, atisane, and hetisane structure.

Table 1 presents data on the acute toxicity of the studied compounds from experiments on white mice through i.v. and i.p. administration. The change of toxicity of the compounds is shown as a function of the carbon skeleton and nature and location of substituents.

Three groups of very toxic compounds can be identified among known DA with the lycoctonine skeleton. These are highly toxic aconitine (**1**) and its analogs, methyllycaconitine (**2**) and related compounds, and lappaconitine (**3**) and aklaloids of similar structure. The toxic properties of the first two groups have been investigated by many researchers and have been proposed as the pharmacophores responsible for the specific properties [10, 13-15].

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TABLE 1. Acute Toxicity and Local Anesthetic Activity of Diterpenoid Alkaloids

Alkaloid, ref.	Toxicity in mice, LD_{50}, mg/kg		Solution conc., %	n	Anesthesia, min., M ± m	
	i.v.	i.p.			onset time	duration
Lappaconitine (**3**) [28]	5.9 (6.1)	15.5	0.1	6	8±0.62	150±3.5
			0.25	10	7±0.21	240±3.0
			0.5	10	5±0.16	310±4.32
			1.0	8	4±0.19	540±7.95
Karakoline (**4**) [16]	51.5	300.0	1.0	5	0	0
1-*O*-Acetylkarakoline (**5**) [17]*	125.3	-	1.0	5	0	0
1-*O*-Benzoylkarakoline(**6**) [17]*	21.8	130	0.25	6	5±0.53	18±1.06
			0.5	6	3±0.35	30±1.41
			1.0	6	2±0.35	45±2.46
1-*O*-Benzoyl-14-*O*-acetylkarakoline (**7**)*	36.3	135	0.25	6	5±0.36	18±1.23
			0.5	6	3±0.25	35±1.76
			1.0	6	1.5±0.16	60±2.29
1-*O*-Acetyl-14-*O*-benzoylkarakoline (**8**)*	8.5	-	0.5	4	0	0
			1.0	8	4.3±0.18	5.8±0.17
Isotalatisidine (**9**) [18]	40.1	170	1.0	5	0	0
Condelphine (14-*O*-acetylisotalatisidine) (**10**) [19]	18.5	-	1.0	5	0	0
1-*O*-Benzoylisotalatisidine (**11**)*	25.3	120	0.25	6	5±0.35	10±0.53
			0.5	6	5±0.28	14±0.88
			1.0	6	4±0.18	20±1.05
1-*O*-Benzoylcondelphine	51.4	250	0.5	4	0	0
(1-*O*-Benzoyl-14-*O*-acetylisotalatisidine) (**12**)*			1.0	6	5.6±0.52	10±0.71
Talatisamine (**13**) [19]	110.0	>300	1.0	5	0	0
14-*O*-Acetyltalatisamine (**14**) [19]	70.7	-	1.0	4	0	0
14-*O*-Benzoyltalatisamine (**15**) [20]	25.0	122.5	0.5	4	0	0
			1.0	8	3.9±0.26	10±0.53
Browniine (**16**) [21]	70	450	1.0	5	0	0
14-*O*-Acetylbrowniine (**17**) [22]	57	300	1.0	5	0	0
14-*O*-Benzoylbrowniine (**18**) [23]	17.5	125	0.5	5	0	0
			1.0	6	5.6±0.24	7±0.44
Delcosine (**19**)	108.7	>200	1.0	4	0	0
14-*O*-Benzoyldelcosine (**20**) [23]	35.1	>100	1.0	6	5.4±0.51	8.2±0.52
14-*O*-Benzoyldictyocarpine (**21**) [24]	22.1	100	1.0	5	4.3±0.32	12±0.38
Aconine (**22**) [25]	200	>450	1.0	5	0	0
Benzoylaconine (**23**) [26]	16	>50	1.0	5	6.2±0.4	10±0.6
3,13,15-*O*-Triacetylaconitine (**24**) [27]*	150	>500	1.0	5	0	0
Pyroaconitine (**25**)*	2.5		0.1	6	9±0.8	55±2.1
			0.25	5	6±0.5	74±3.2
Lappaconine (**26**) [28]	195	400	1.0	4	0	0
4,8,9-*O*-Triacetyllappaconine (**27**) [28]	145	300	1.0	4	0	0
N-Deacetyllappaconitine (**28**)*	7.3	35.0	0.1	8	5.5±0.28	50±0.66
			0.25	8	4.5±0.20	75±1.59
			0.5	8	3.1±0.26	100±3.17
			1.0	8	2.4±0.18	120±4.23
Sepaconitine (**29**) [29]	16.5	62.2	0.1	8	5±0.27	58±1.98
			0.25	8	4.1±0.28	88±2.11
			0.5	7	3.6±0.15	75±2.12
			1.0	8	2.1±0.18	100±3.35
Ranaconitine (**30**) [30]	6.2	-	0.1	8	7±0.52	158±3.6
			0.25	8	4.8±0.18	284±4.3
N-Acetylsepaconitine (**31**) [31]	15	-	0.25	8	8.1±0.28	196±2.4
			0.5	8	4.3±0.13	340±4.5
N-Deacetyl-	2.6	7.2	0.1	6	6.6±1.2	136±1.8
N-Dimethyllappaconitine (**32**)*			0.25	6	5.8±0.28	156±2.4

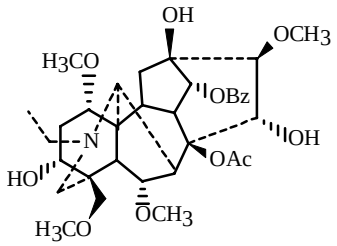
TABLE 1. (continued)

Alkaloid, ref.	Toxicity in mice, LD_{50}, mg/kg		Solution conc., %	n	Anesthesia, min., M ± m	
	i.v.	i.p.			onset time	duration
Septephine (**33**) [32]	4.75	13.22	0.1	6	10.0±0.4	130±1.8
			0.25	6	8.1±0.1	148±2.6
Artecorine (**34**) [33]	20.1	58.0	0.1	6	6.6±1.2	0
			0.25	6	5.4±0.28	88±3.2
Lycoctonine (**35**) [34]	170	>300	1.0	5	0	0
Anthranoyllycoctonine (**36**) [35]	20.1	98.7	1.0	5	0	0
Ajacine (**37**) [35]	9	35.4	1.0	5	0	0
Delectine (**38**) [36]	35.8	>100	1.0	5	0	0
O-Acetyldelectine (**39**) [36]	15.5	>50	1.0	5	0	0
N-Acetyldelectine (**40**) [36]	25.3	>100	1.0	4	0	0
N,O-Diacetyldelectine (**41**)*	12.5	>50	1.0	5	0	0
Delcorine (**42**) [37]	116	590	1.0	5	0	0
Deoxydelcorine (**43**) [38]	46.5	235	1.0	5	0	0
6-*O*-Benzoyldelcorine (**44**)*	45	205	0.25	4	0	0
			0.5	6	6.8±0.88	30±1.41
			1.0	6	3.5±0.53	45±2.1
Eldelidine (**45**) [39]	235	>500	1.0	5	0	0
Eldeline (**46**) [39]	136	>500	1.0	5	0	0
6-*O*-Benzoyleldelidine (**47**)*	16.1	66.0	0.05	8	5±0.39	45±1.85
			0.1	10	3±0.31	105±2.39
			0.25	10	2±0.11	135±1.95
			0.5	10	1±0	210±3.28
Heteratisine (**48**) [40, 41]	180.0	430	1.0	4	0	0
Dehydroheteratisine (**49**) [42]*	165.0	-	1.0	4	0	0
6-*O*-Acetylheteratisine (**50**) [42]*	182.0	-	1.0	4	0	0
6-*O*-Benzoylheteratisine (**51**) [41]	5.0	21.5	0.05	8	4.1±0.26	40±1.98
			0.1	8	3.2±0.19	65±2.65
			0.25	8	2.7±0.06	190±3.05
			0.5	8	1±0	210±3.97
6-*O*-Anisoylheteratisine (**52**) [42]*	6.0	38.7	0.1	8	5.2±0.24	32±0.67
			0.25	8	3.5±0.13	45±1.73
			0.5	8	1.5±0.06	128±1.99
6-*O*-Furoylheteratisine (**53**) [42, 43]*	16.1	68	0.1	8	4.3±0.13	48±0.93
			0.25	8	2.7±0.07	96±2.51
			0.5	8	1±0	180±2.91
6-*O*-Veratroylheteratisine (**54**) [10, 44]*	42.5	-	0.25	6	0	0
			0.5	8	3.4±0.19	36.4±4.0
6-*O*-Nitrobenzoylheteratisine (**55**) [42]*	27.5	-	0.25	6	0	0
			0.5	8	4.8±0.24	41.6±1.98
Songorine (**56**) [45]	142.5	480	1.0	6	0	0
Dihydrosongorine (**57**) [4]	120.0	450	1.0	5	0	0
1-*O*-Acetylsongorine (**58**) [50]*	150.0	420.0	1.0	5	0	0
1,15-*O*-Diacetylsongorine (**59**) [50]*	131.0	805.0	1.0	5	0	0
Songorine *N*-oxide (**60**) [48]	550.0	>2000	1.0	5	0	0
Napelline (**61**) [45]	88.0	280	1.0	5	0	0
12-Epinapelline (**62**) [47]	82.0	>250	1.0	5	0	0
12-*O*-Acetylnapelline (**63**) [51]	101.0	-	1.0	5	0	0

TABLE 1. (continued)

Alkaloid, ref.	Toxicity in mice, LD_{50}, mg/kg		Solution conc., %	n	Anesthesia, min., M ± m	
	i.v.	i.p.			onset time	duration
1-*O*-Benzoylnapelline (**64**) [50]*	30.0	135	0.1	8	2.3±0.13	36.2±0.92
			0.25	8	1.6±0.08	61.0±1.01
			0.5	8	1±0.08	75.2±1.8
			1.0	8	1±0	76.8±3.6
Napelline *N*-oxide (**65**) [49]	725.0	>2000	1.0	4	0	0
Tadzhaconine (**66**) [52]	12.8	-	0.05	6	3.7±0.21	40±0.93
			0.1	6	2.2±0.18	58±2.1
			0.25	6	1.4±0.12	96±2.3
			0.5	6	1±0.1	210±3.97
Zeravschanizine (**67**) [53]	34.1	160	0.25	8	3.1±0.25	86±2.2
			0.5	8	2.4±	94±2.5
			1.0	8	2.2±0.18	115±2.6
Hetisine (**68**) [41]	26.2	-	0.5	6	7.4±0.36	12±1.6
			1	8	2.5±0.25	25±1.41
Nominine (**69**) [53]	68.0	-	0.5	6	8.1±0.24	14±1.6
			1	8	2.2±0.18	34±1.24
Dihydroatisine (**70**) [53]	38	88	0.1	3	0	0
			0.25	6	1±0.1	30.2±1.2
			0.5	8	3±0.55	34±1.76
Atidine (**71**) [39]	58.1	-	0.5	6	8.4±0.21	26±1.3
			1	8	2.3±0.17	55±1.9
Septedine (**72**) [55]	43.5	-	0.25	6	3.6±0.18	20±1.2
			0.5	6	3.1±0.26	28±0.24
			1.0	6	2.4±0.18	54±1.76
Dictysine (**73**) [56]	165	-	1.0	5	0	0
Dictysine acetonid (**74**) [56]	45	-	1.0	5	0	0
Cocaine (**75**)	29.5	80	0.1	10	0	0
			0.25	20	1.16±0.03	11.5±0.28
			0.5	20	1±0.0	13.6±0.44
			1.0	12	1±0.0	13.7±0.35

Compounds **6**, **7**, **11**, **12**, **18**, **44**, **54**, and **55** exhibited local anesthetic activity that was evaluated by the Setnikar method (1966); n is the number of experiments; *synthetic compounds; 0, no local anesthetic effect.



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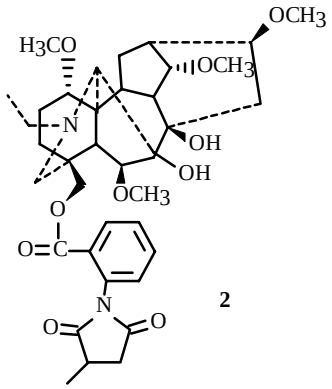

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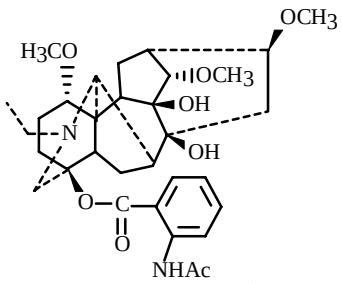
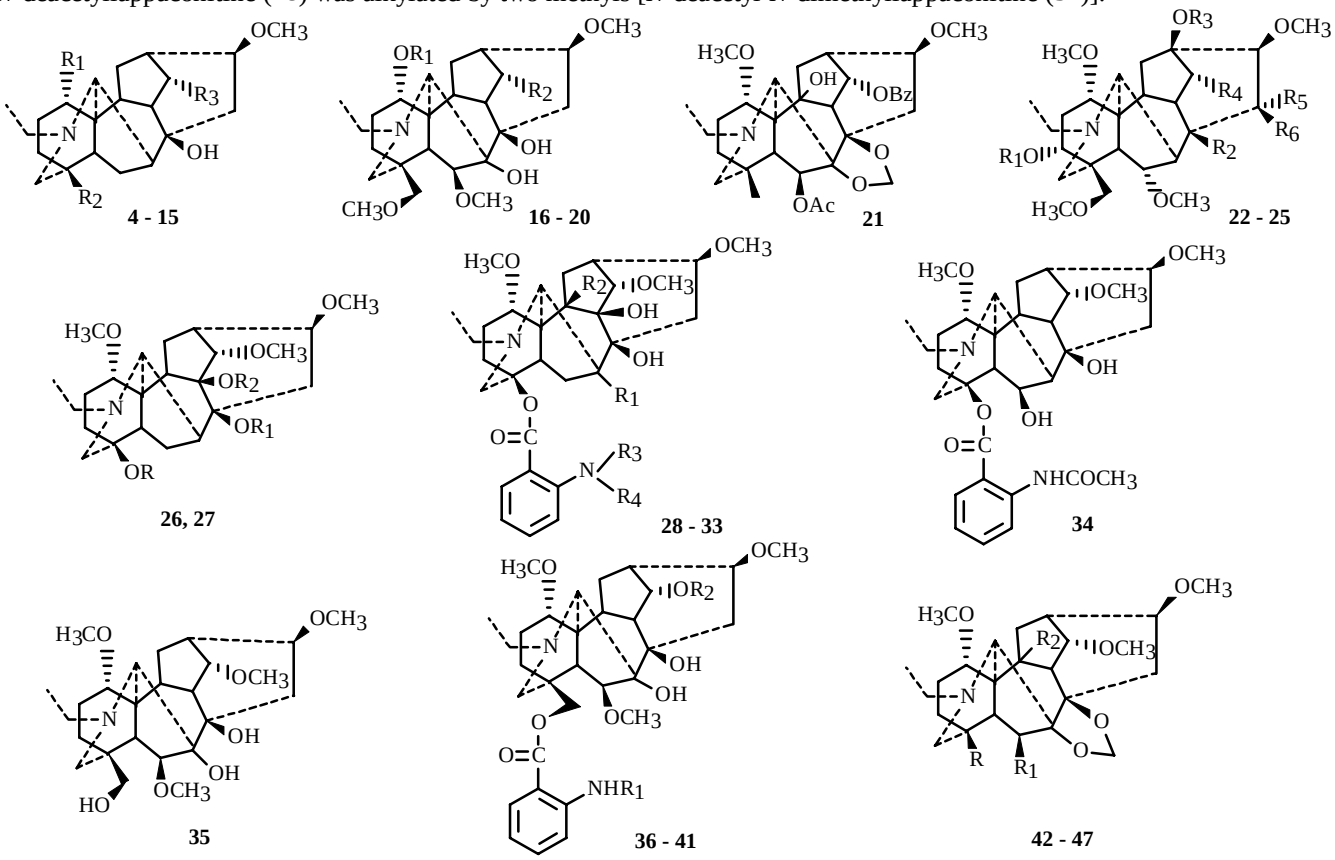


3

The toxic properties of 10 alkaloids from the lappaconitine group and their derivatives were examined (**3**, **26**-**34**). Lappaconitine has the lycoctonine skeleton with an *N*-ethyl group and contains an acetylanthranilic acid on C-4, a diol system on C-8 and C-9, and methoxyls on C-1, C-14, and C-16. Table 1 shows that the toxicity decreased sharply upon removing the ester [lappaconine (**26**)]. Adding additional hydroxyls in the 7- or 10-position [ranaconitine (**30**) and sepaconitine (**29**)] also

reduced the toxicity. The poisonous properties decreased upon saponifying the acetyl of the ester [*N*-deacetyllappaconitine (**28**)] whereas replacing the acetyl of the acetylanthranilic acid in lappaconitine (**3**) by methyl increased the toxic properties [septephine (**33**)] only slightly. The toxicity more than doubled when the amino group of the anthranilic acid in *N*-deacetyllappaconitine (**28**) was alkylated by two methyls [*N*-deacetyl-*N*-dimethyllappaconitine (**32**)].



4: $R_1 = R_3 = OH$, $R_2 = CH_3$; **5:** $R_1 = OAc$, $R_2 = CH_3$, $R_3 = OH$; **6:** $R_1 = OBz$, $R_2 = CH_3$, $R_3 = OH$
7: $R_1 = OBz$, $R_2 = CH_3$, $R_3 = OAc$; **8:** $R_1 = OAc$, $R_2 = CH_3$, $R_3 = OBz$; **9:** $R_1 = R_3 = OH$, $R_2 = CH_2OCH_3$
10: $R_1 = OH$, $R_2 = CH_2OCH_3$, $R_3 = OAc$; **11:** $R_1 = OBz$, $R_2 = CH_2OCH_3$, $R_3 = OH$; **12:** $R_1 = OBz$, $R_2 = CH_2OCH_3$, $R_3 = OAc$
13: $R_1 = OCH_3$, $R_2 = CH_2OCH_3$, $R_3 = OH$; **14:** $R_1 = OCH_3$, $R_2 = CH_2OCH_3$, $R_3 = OAc$
15: $R_1 = OCH_3$, $R_2 = CH_2OCH_3$, $R_3 = OBz$; **16:** $R_1 = CH_3$, $R_2 = OH$; **17:** $R_1 = CH_3$, $R_2 = OAc$; **18:** $R_1 = CH_3$, $R_2 = OBz$
19: $R_1 = H$, $R_2 = OH$; **20:** $R_1 = H$, $R_2 = OBz$; **22:** $R_1 = R_3 = R_6 = H$, $R_2 = R_4 = R_5 = OH$
23: $R_1 = R_3 = R_6 = H$, $R_2 = R_5 = OH$, $R_4 = OBz$; **24:** $R_1 = R_3 = Ac$, $R_2 = R_5 = OAc$, $R_4 = OBz$, $R_6 = H$
25: $R_1 = R_2 = R_3 = H$, $R_4 = OBz$, R_5-$R_6 = O$; **26:** $R = R_1 = R_2 = H$; **27:** $R = R_1 = R_2 = Ac$; **28:** $R_1 = R_2 = R_3 = R_4 = H$
29: $R_1 = R_3 = R_4 = H$, $R_2 = OH$; **30:** $R_1 = OH$, $R_2 = R_3 = R_4 = H$; **31:** $R_1 = R_4 = H$, $R_2 = OH$, $R_3 = Ac$
32: $R_1 = R_2 = H$, $R_3 = R_4 = CH_3$; **33:** $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$; **36:** $R_1 = H$, $R_2 = CH_3$; **37:** $R_1 = Ac$, $R_2 = CH_3$
38: $R_1 = R_2 = H$; **39:** $R_1 = H$, $R_2 = Ac$; **40:** $R_1 = Ac$, $R_2 = H$; **41:** $R_1 = R_2 = Ac$; **42:** $R = CH_2OCH_3$, $R_1 = OH$, $R_2 = H$
43: $R = CH_2OCH_3$, $R_1 = R_2 = H$; **44:** $R = CH_2OCH_3$, $R_1 = OBz$, $R_2 = H$; **45:** $R = CH_3$, $R_1 = R_2 = OH$; **46:** $R = CH_3$, $R_1 = OAc$, $R_2 = OH$
47: $R = CH_3$, $R_1 = OBz$, $R_2 = OH$

In general for DA, the toxicity increased in the order aminoalcohols—aminoalcohol acetates—esters of monoaromatic acids. The extent of the toxicity increase depended on the mutual location and nature of the *O*-aromatic ester substituent and other oxygen functions in addition to the steric and electronic properties of the *N* atom.

Local anesthetic activity of DA was studied using surface anesthesia of rabbit eye cornea by determining the corneal reflex after administration into the conjunctival sac of 0.1-0.2 mL of various concentrations of test compound (from 0.05 to 1% solutions) according to the onset time, intensity, and duration of anesthesia and the presence of irritation. The activities of the compounds were compared with that of cocaine. The most active compounds identified by these experiments were investigated by conductance and trunk anesthesia methods. Local anesthetic activities were compared with those of novocaine and lidocaine.

Among alkaloids with the lycoctonine skeleton, amino alcohols and their acetates did not cause anesthesia at concentrations up to 1% in solution according to the adopted criteria.

Compounds with distinct local anesthetic activity were found among C-1, C-4, C-6, and C-14 esters of aromatic acids. The activity and duration of the local anesthetic activity of the DA depended on the location and nature of the *O*-aromatic substituent, the mutual location of the *O*-containing groups, and the basicity of the *N* atom.

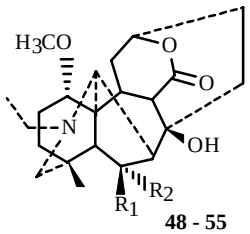
Among alkaloids containing an *O*-aromatic substituent, C-18-*O*-aromatic substituted derivatives of lycoctonine [anthranoyllycoctonine (**36**) and ajacine (**37**)] and delectine (**38**), *O*-acetyldelectine (**39**), *N*-acetyldelectine (**40**), and *N*,*O*-diacetyldelectine (**41**) did not exhibit local anesthetic activity.

Compounds containing an *O*-aromatic substituent in the C-14 position (**8**, **15**, **18**, **20 21**, **23**) exhibited weak local anesthetic activity. C-1 *O*-benzoyl derivatives of karakoline and isotalatisidine (**6**, **7**, **11**) showed a slightly greater local anesthetic activity. These compounds had the same activity as cocaine, exceeded it in duration, and had slower rates of anesthesia onset (Table 1).

C-4 *O*-aromatic esters of lappaconine (**3**, **28**-**34**) and C-6 esters of eldelidine and delcorine (**47** and **44**) had the highest local anesthetic activity. Their activity and duration were greater than those of cocaine but the rates of anesthesia onset were slower.

Alkaloids of similar structure containing anthranilic or acetylanthranilic acid in C-4 or C-18 positions differed qualitatively in properties. Whereas **3** and **28**-**34** possessed distinct local anesthetic activity, **36**-**41** did not exhibit an analgesic effect.

Compounds with local anesthetic activity differed in activity, rate of onset, intensity, and duration of anesthesia. The most active alkaloids were sepaconitine (**29**), ranaconitine (**30**), lappaconitine (**3**), and 6-*O*-benzoyleldelidine (**47**), which caused anesthesia initially with a 0.1% solution. As the concentration increased, the latent period of onset decreased and the intensity and duration of anesthesia decreased. At concentrations of 1%, they caused corneal dryness and dilation of the pupils. Using structural analogs of lappaconitine (**3** and **28**-**34**) as examples, it can be seen that the nature of the C-4 substituent has a marked effect on the intensity and duration of local anesthetic activity.



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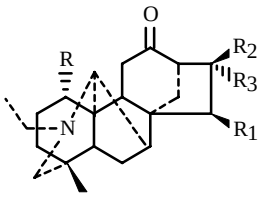
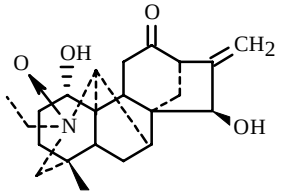
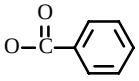
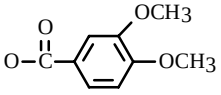


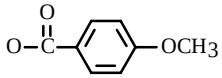
56 - 59

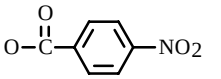


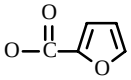
60

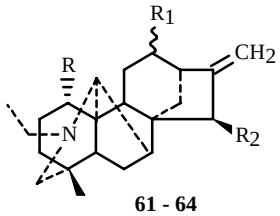
51: R_1 = 

54: R_1 = 

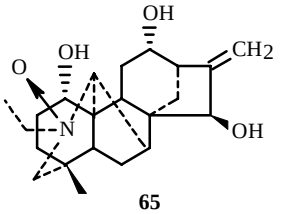
52: R_1 = 

55: R_1 = 

53: R_1 = 



61 - 64



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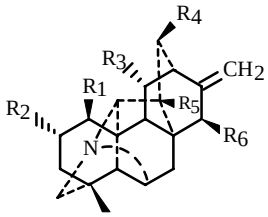
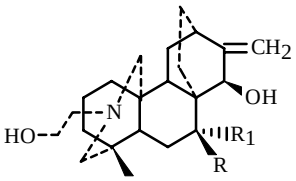
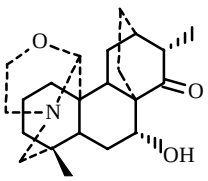


66 - 69



70 - 71



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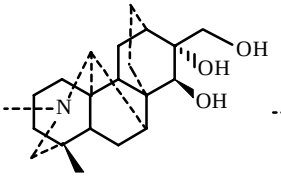

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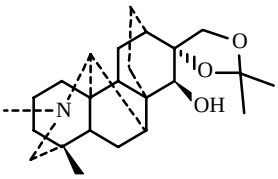

74

48: R_1 = OH, R_2 = H; **49:** R_1-R_2 = O; **50:** R_1 = OAc, R_2 = H; **51 - 55**: R_2 = H

56: R = R_1 = OH, R_2-R_3 = CH_2; **57:** R = R_1 = OH, R_2-R_3 = CH_2; **58:** R = OAc, R_1 = OH, R_2-R_3 = CH_2

59: R = R_1 = OAc, R_2 -R_3 = CH_2; **61:** R = R_2 = OH, R_1 = α-OH; **62:** R = R_2 = OH, R_1 = β-OH; **63:** R = R_2 = OH, R_1 = α-OAc

64: R = OBz, R_1 = α-OH, R_2 = OH; **66:** R_1 = R_3 = OAc, R_2 = OBz, R_4 = OH, R_5 = R_6 = H

67: R_1 = R_6 = H, R_2 = OAc, R_3 = R_5 = OH, R_4 = OBz; **68:** R_1 = R_5 = R_6 = H, R_2 = R_3 = R_4 = OH

69: R_1 = R_2 = R_3 = R_4 = R_5 = H, R_6 = OH; **70:** R = R_2 = H; **71:** R-R_1 = O

A comparison of the activities of 6-*O*-benzoyleldelidine (**47**) and 6-*O*-benzoyldelcorine (**44**) showed that not only the nature and location of the aromatic substituent had an effect on the local anesthetic activity but also the mutual location of the *O*-containing groups in the lycoctonine skeleton. 6-*O*-Benzoyldelcorine (**44**) contains a C-4 methoxy and no substituent on C-10 whereas 6-*O*-benzoyleldelidine (**47**) contains a C-10 hydroxyl and a C-4 methyl. The local anesthetic activity of 6-*O*-benzoyleldelidine is much greater than that of 6-*O*-benzoyldelcorine.

Heteratisine (**48**) and its C-6-*O*-acetyl derivative (**50**) at concentrations up to 1% did not exhibit local anesthetic activity whereas the C-6-*O*-aromatic ester of heteratisine had distinct local anesthetic activity that also depended on the nature of the *O*-aromatic substituent. 6-*O*-Benzoylheteratisine (**51**) and 6-*O*-furoylheteratisine (**53**) exhibited the greatest activities; 6-*O*-veratroylheteratisine (**54**) and 6-*O*-*p*-nitrobenzoylheteratisine (**55**), the lowest. Compounds **51**-**55** had activities and durations of anesthesia that exceeded those of cocaine but had slower rates of onset of anesthesia.

Compounds with distinct local anesthetic activity were found among alkaloids with the napelline, hetisane, and atisane skeletons. Compounds with distinct local anesthetic activity were amino alcohols (**68**-**72**) and esters of amino alcohols (**66** and **67**). Amino alcohols had lower activities and durations of action than alkaloids with ester groups. Like for alkaloids with the lycoctonine and heteratisine skeletons, the latent period for onset, intensity, and duration of anesthetic activity for the studied compounds depended directly on concentration. In contrast with compounds with lycoctonine and heteratisine skeletons, the latent period for onset of anesthesia was shorter. 1-*O*-Benzoylnapelline (**64**) and tadzhaconine (**66**) had the highest activities of the studied alkaloids. The activity and duration of local anesthetic activity of these alkaloids were greater than those of cocaine; the rates of onset and intensity of anesthesia, similar to those of it.

The local anesthetic activity of the most active alkaloids of the various structural types [lappaconitine (**25**), 6-*O*-benzoyleldelidine (**45**), 6-*O*-benzoylheteratisine (**49**), 1-*O*-benzoylnapelline (**62**), and tadzhaconine (**64**)] was studied using conductance and trunk methods of anesthesia on rabbits and cats and was compared with those of novocaine and lidocaine.

Administration (intracutaneous and s.c.) of solutions (0.05 and 0.1%) of these compounds to rabbits temporarily decreased the sensitivity of skin sections and increased the threshold of pain irritation by several hours to a day. Their activities and durations of action were greater than those of novocaine and lidocaine. Ranaconitine (**30**) and lappaconitine (**3**) had the longest duration of action; 6-*O*-benzoyleldelidine (**47**), 6-*O*-benzoylheteratisine (**51**), 1-*O*-benzoylnapelline (**64**), and tadzhaconine (**66**), the highest activity. The anesthetic activity of these compounds was evident upon s.c. administration of 0.001-0.01% solutions with durations from 80 to 160 min. Novocaine and lidocaine solution (0.1%) did not have anesthetic activity. The duration of anesthesia of a 0.5% solution of novocaine was 54 min; of a 0.5% solution of lidocaine, 85 min.

The aforementioned compounds were effective for trunk anesthesia at concentrations of 0.1-0.5%. A cotton ball soaked with a solution of these compounds that was applied to the first trunks or injected near a nerve fiber caused complete blockage of afferent and efferent pulses and loss of pain sensitivity.

Thus, the screening of DA of various structural types and their derivatives for local anesthetic activity identified 26 compounds with distinct activity for surface anesthesia in rabbit eye cornea. Of these, 15 compounds had activities and durations of action that were greater than those of cocaine. However, their rates of onset of anesthesia were slower than that of cocaine. The exceptions were 1-*O*-benzoylnappeline (**64**) and tadzhaconine (**66**), which had rates of onset similar to that of cocaine and activities and durations of anesthesia that were higher. Compounds with high anesthetic activity were found among representatives of the various structural types.

EXPERIMENTAL

The resorptive activity and acute toxicity were studied using white mongrel mice of mass 18-22 g. Compounds were administered i.v. and i.p. in 4-5 increasing doses. Each dose was tested in 5-6 animals.

Local anesthetic activity was studied in rabbits of mass 3-4 kg. The effect on terminal anesthesia was studied by the Renier—Valette method on rabbit eye cornea by determining the corneal reflex to touching by hair after dropping into the conjunctival sac a solution (0.1 mL, 0.01-1%) of the test compound. Each concentration was tested on 4-10 animals taking into account the time of onset, intensity, and duration of anesthesia.

The results were treated statistically by the literature method [57]. The effect on infiltration anesthesia was studied by the Bulbring—Waida method. Anesthetic activity was evaluated by intracutaneous and s.c. administration of the compounds. The effect of the compounds on trunk anesthesia was studied on cats by applying to the neck trunk of the exciting nerve a solution (0.1-0.5%) of the alkaloids using a cotton ball.

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