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QUATERNARY DERIVATIVES OF α- AND β-SCOPODONNINES AND THEIR PHARMACOLOGIC ACTIVITY

N. A. Razzakov, A. Vakhabov, and S. F. Aripova

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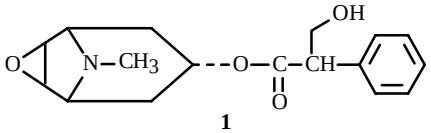
Several quaternary alkyl halides were synthesized from dimeric tropane alkaloids α- and β-scopodonnines, which were prepared by dimerization of hyoscine. Their pharmacologic activities were studied.

Key words: tropane alkaloids, α- and β-scopodonnines, alkyl halides, myorelaxants.

Plants producing tropane alkaloids have for a long time attracted the attention of chemists because the high physiological activity of this class of natural compounds is well known. We isolated about 30 alkaloids, including four dimeric bases, during chemical research of the alkaloid composition of plants from the genera *Datura* (*D. stramonium, D. inoxia*), *Hyoscyamus* (*H. niger, H. pusillus*), *Mandragora* (*M. turcomanica*), and *Physochlaina* (*P. alaica*) of the Solanaceae family [1].

A pharmacologic investigation of certain tropane alkaloids with a tertiary N atom (6-hydroxyhyoscyamine, α- and β-belladonnines) showed that they exhibit distinct *m*-cholinolytic activity. A study of quaternary derivatives of the dimeric tropane alkaloids α- and β-belladonnines found that they posses myorelaxant properties [2].

In order to search for a more active compound and to determine the structure—activity relationship for the physiological activity of the compounds, we synthesized a homologous series of alkyl halides from α- and β-scopodonnines, which are minor natural constituents that are easily obtained from hyoscyamine [3] analogously to α- and β-belladonnines. The products of hyoscine dimerization, α- and β-scopodonnines, were isolated by column chromatography over Al_2O_3. Elution of the column by ethylacetate isolated α-scopodonnine; by $CHCl_3$, β-scopodonnine [4, 5].



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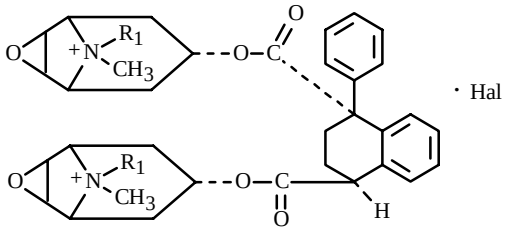
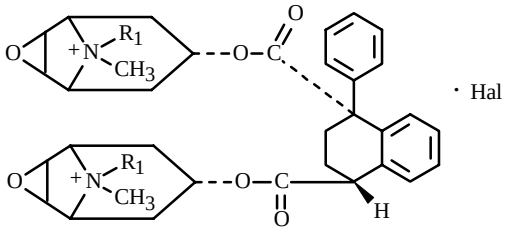


α: **3, 5, 6**



β: **4, 7, 8,**

	R_1	Hal		R_1	Hal
2: α- +β-	CH_3	$2I^-$	**7:** β-	C_2H_5	$2Cl^-$
3: α-	CH_3	$2I^-$	**8:** β-	C_2H_5	$2I^-$
4: β-	CH_3	$2I^-$	**9:** α- + β-	C_3H_7	$2I^-$
5: α-	C_2H_5	$2Cl^-$	**10:** α- + β-	$CH(CH_3)_2$	$2I^-$
6: α-	C_2H_5	$2I^-$	**11:** α- +β-	C_4H_9	$2I^-$

S. Yu. Yunusov Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (99871) 120 64 75, e-mail: cnc@icps.org.uz. Translated from Khimiya Prirodnykh Soedinenii, No. 2, pp. 162-163, March-April, 2003. Original article submitted March 4, 2003.

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TABLE 1. Myorelaxant Activity of Quaternary Derivatives of α- and β-Scopodonnines (**2**-**11**) Administered Internally

Compound	LD_{50}, mg/kg, dose causing	
	cessation of breathing in 50% of intact mice	loss of neuromuscular conductivity in 50% of anesthetized cats
2	1.3	0.6-1.0
3	7.0	3.0-5.0
4	1.0	0.3-0.5
5	1.0	0.5-0.7
6	6.0	3.0-5.0
7	1.0	0.5-0.6
8	1.0	0.5-0.8
9	10.0	5.0-8.0
10	8.0	5.0-7.0
11	20.0	10.0-15.0

Bisalklyhalides (CH_3I and C_2H_5I) were synthesized from the isomers and their equilibrium mixture and were tested for myorelaxant activity. In addition to the bisethyliodides of α- and β-scopodonnines, the corresponding bisethylchlorides, which were prepared by halide exchange with freshly precipitated AgCl, were investigated. The bispropyliodides, bisisopropyliodides, and bisbutyliodides were prepared from a mixture of α- and β-scopodonnines.

Table 1 contains the experimental results from the study of the myorelaxant activity of the synthesized compounds.

It can be seen that the myorelaxant activity of the compounds decreases as the molecules increase in mass on going from the bismethyliodides of α- and β-scopodonnines (**2**) to the corresponding bispropyliodides and bisbutyliodides (**9**, **11**). It is also noteworthy that the activity sharply changes as a function of the α- and β-isomerism (**3**-**7**). Among the studied compounds, the bismethyliodides and bisethyliodides synthesized from the β-isomer are promising. The most active compound was β-scopodonnine bismethyliodide, which has distinct myorelaxant activity and other properties that are valuable in practice. Thus, in contrast with existing antidepolarizing myorelaxants, its activity is short-lived. At effective doses, it affects substantially the hemodynamics. In difference to *d*-tubocurarine [7], it has some antihistamine activity [7].

EXPERIMENTAL

TLC was performed on plates with an attached layer of KSK silica gel containing gypsum. Column chromatography used L 40/100 silica gel.

Chromatography used the solvent systems $CHCl_3$:CH_3OH (9:1, 1) and $CHCl_3$:CH_3OH:NH_4OH (conc.) (4:1:0.2, 2).

Melting points were determined on a Kofler block.

Preparation of α- and β-Scopodonnines. Hyoscine (**1**, 1.0 g) was heated for 6 h at 110-120°C (TLC monitoring). After the reaction was complete, the brown reaction mixture was dissolved in H_2SO_4 (30 mL, 5%) and treated three times with $CHCl_3$ (10 mL each). The combined $CHCl_3$ extracts were dried over anhydrous Na_2SO_4 and evaporated. The solid was dissolved in water, made basic with NH_4OH (10%), extracted with $CHCl_3$, dried, and evaporated. The solid was apohyoscine, R_f 0.75 (system 1).

The H_2SO_4 solution of alkaloids was made basic with NH_4OH (conc.), extracted with $CHCl_3$, dried, and evaporated. The total alkaloids (0.7 g) were chromatographed over a column of Al_2O_3 with elution by hexane, ethylacetate, and $CHCl_3$. The ethylacetate fractions yielded crystals (0.3 g) with mp 178-179°C, R_f 0.55 (α-scopodonnine). The $CHCl_3$ eluates produced crystals (0.15 g) with mp 189-191°C, R_f 0.46 (β-scopodonnine).

Preparation of Bisalkylhalides of α- and β-Scopodonnines (General Method). A solution of α- or β-scopodonnine (0.1 g) in CH_3OH or acetone was treated with an excess of alkyl iodide. The mixture was boiled on a water bath for 1 h and left overnight. The precipitat of α- or β-scopodonnine bisalkyliodide was separated and dried.

α-Scopodonnine bismethyliodide (3) was prepared by the above method, mp 204-206°C.

β-Scopodonnine bismethyliodide (4), mp 195-196°C.

α-Scopodonnine bisethyliodide (6), mp 183-184°C.

α-Scopodonnine bisethylchloride (5). α-Scopodonnine bisethyliodide (0.1 g) in CH_3OH (10 mL) was treated with freshly precipitated AgCl (0.1 g). The suspension was shaken for 4 h. The precipitate of AgI was separated. The CH_3OH mother liquor was evaporated to form crystals (0.07 g) with mp 101-102°C.

β-Scopodonnine bisethyliodide (8), mp 201-202°C.

β-Scopodonnine bisethylchloride (7), mp 156-157°C (prepared analogously to α-scopodonnine bisethylchloride).

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