SYNTHESIS OF CARBAMATES OF AMINO ALCOHOLS OF PYRROLIZIDINE AND QUINAZOLIDINE ALKALOIDS

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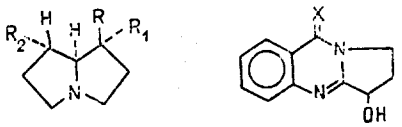
1-Methylpyrrolizidine and quinazoline alkaloids are widely distributed in plants [1, 2]. Some semisynthetic derivatives of the 1-methylpyrrolizidine alkaloids possess curaremimetic [3] and total anaesthetic properties [4]; many carbamates of heterocyclic compounds, and also quinazoline derivatives and some quinazoline alkaloids exhibit various physiological and pesticidal activities [5, 6].

In order to obtain potentially pharmacologically active compounds, we have synthesized carbamates of some cleavage products of 1-methylpyrrolizidine alkaloids and of amino alcohols of the quinazoline series by the reaction of alkyl and aryl isocyanates and of hexamethylene diisocyanate with the corresponding alcohols.s. As the amino alcohols of the 1-pyrrolizidine series we used the stereoisomeric trachelanthamidine (I) and isoretronecanol (II) and also hydroxyheliotropidane (III), and of quinazolidine derivatives the alkaloids peganine (IV) and vasicinone (V).



I. $R=R_2=H$; $R_1=CH_2OH$ IV. $X=H_2$
II. $R=CH_2OH$; $R_1=R_2=H$ V $X=O$
III. $R=CH_3$; $R_1=H$; $R_2=OH$

The reactions of the above-mentioned compounds (I–V) with butyl and with p-chlorophenyl isocyanates were performed without catalysts in benzene, chloroform, and acetone solutions or in the absence of solvents at room temperature or with the boiling of the reaction mixture:

The reaction of one equivalent of hexamethylene diisocyanate with two equivalents of amino alcohol formed bis-carbamates:

$$ROH+ONC-(CH_2)_6-NCO+HOR \longrightarrow ROCONH(CH_2)_6-NH-COOR,$$

R = residue of (I) or (III-V).

The structure of the compounds obtained was shown by elementary analysis and IR spectroscopy. Their IR spectra have absorption bands in the 1640-1695, 1730-1735, and 3315-3350 cm^{-1} regions corresponding to the NHCOO group.

The yields and conditions of obtaining the amino alcohol carbamates of the 1-methylpyrrolizidine and quinazolidine alkaloids are given in Table 1.

The stereoisomeric trachelanthamidine (I) and isoretronecanol (II) react with butyl isocyanate under different conditions. Thus, while the latter compounds react with (II) at room temperature, (I) reacts with it only on heating (75-80°C). The difference in the reactivities of (I) and (II) is apparently due to the formation of an intramolecular hydrogen bond between the nitrogen atom and the hydroxy group in (I) the cleavage of which requires additional energy; consequently (I) reacts with greater difficulty then (II).

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TABLE 1. Properties of the Carbamates of Amino Alcohols of 1-Methylpyrrolizidine and Quinazolidine Alkaloids

	Isocyanate	Reaction product	Reaction condition			Yield, %	mp, °C	Empirical formula
			solvent	temperature	time, h			
I	H–C_4H_9NCO	Trachelanthamidine n-butylcarbamate	Benzene	80	0,5	90	107–108 (acetone)	$C_{13}H_{24}O_2N_2$
II	H–C_4H_9NCO	Isoretronecanol n-butylcarbamate	"	20	2	88	145–146 (acetone)	$C_{13}H_{24}O_2N_2$
III	p–Cl–C_6H_4NCO	Hydroxyheliotridane p-chlorophenylcarbamate	"	80	2	82	Above 200° (ethanol)	$C_{15}H_{19}ClO_2N_2$
I	$ONC(CH_2)_6NCO$	Hexamethylenedicarbamate of trachelanthamidine		20	0,2	82	64–65 (Acetone + petroleum ether)	$C_{24}H_{42}O_4N_4$
III	"	Hexamethylenedicarbamate of hydroxyheliotridane	Acetone	20	0,4	80		$C_{24}H_{42}O_4N_4$
IV	H–C_4H_9NCO	Peganine n-butylcarbamate	Chloroform	65	4	78	162 (ethanol)	$C_{16}H_{21}O_2N_3$
IV	p–Cl–C_6H_4NCO	Peganine p-chlorophenylcarbamate	Benzene	80	4	88	240–241 (ethanol)	$C_{18}H_{16}ClO_2N_3$
V	H–C_4H_9NCO	Vasicinone n-butylcarbamate	"	"	3	76	166–167 (ethanol)	$C_{16}H_{19}O_3N_3$
IV	$ONC(CH_2)_6NCO$	Hexamethylenedicarbamate of peganine	"	"	2	84	155–156 (ethanol)	$C_{30}H_{36}O_4N_6$
V	"	Hexamethylenedicarbamate of vasicinone	"	"	5	83	182–183 (ethanol)	$C_{30}H_{32}O_6N_6$

In an investigation of the anticholinesterase properties of the carbamates of peganine it was found that they inhibit the activity of the acetyl- and butylcholinesterases of the blood and brain. The carbamates of vasicinone possess a slight inhibiting activity; the carbamates of trachelanthamidine, isoretronecanol, and hydroxyheliotridane possess no anticholinesterase activity.

EXPERIMENTAL

The alkaloids peganine (IV) and vasicinone (V) were given to us by S. Yu. Yunusov and M. V. Telezhenetskaya.

Trachelanthamidine (I) was obtained by the hydrolysis of the alkaloid trachelanthamine [7], and isoretronecanol (II) by the hydrolysis of the alkaloid lindelofine [8]. Hydroxyheliotropidane was obtained by the Adams reduction of rinderine.

Trachelanthamidine n-Butylcarbamate. A benzene solution of 0.2 g of (I) was treated with 0.2 g of butyl isocyanate and the mixture was heated at 75-80°C for 30 min. The benzene layer was poured off, and the oily residue was crystallized from acetone. Yield 0.3 g.

Reaction of Hydroxyheliotropidane (III) with Hexamethylene Diisocyanate. To a solution of 1.5 g of (III) in 10 ml of dry acetone was added 0.8 g of hexamethylene diisocyanate in 5 ml of acetone. After 10-15 minutes, the solvent was distilled off and the residue was chromatographed on a column of alumina (with benzene–chloroform as the eluent). The yield of the hexamethylenedicarbamate of hydroxyheliotridane was 1.8 g, R_f 0.80 (chloroform–methanol, 10 : 1). Dimethiodide mp 181-183°C.

Peganine p-chlorophenylcarbamate. A suspension of 1.0 g of (IV) and 0.8 g of p-chlorophenyl isocyanate in 20 ml of dry benzene was boiled for 4 h; the (IV) first began to dissolve, and then the reaction product began to precipitate. The latter was filtered off, washed with benzene, and recrystallized from ethanol. Yield 1.7 g.

SUMMARY

Previously undescribed mono- and dicarbamates of pyrrolizidine and quinazolidine amino alcohols have been obtained by the reaction of mono- and diisocyanates with the corresponding alcohol derivatives of the alkaloids.

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STRUCTURE OF NUPHLEINE – AN ALKALOID FROM Nuphar luteum

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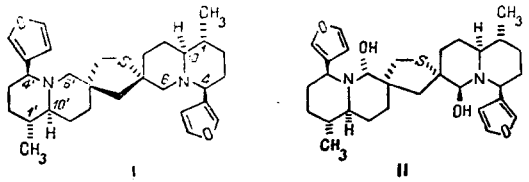
We have previously [1, 2] reported the isolation from the dry rhizomes of Nuphar luteum L. (European cowlily) of a new sulfur-containing alkaloid – nuphleine $C_{30}H_{42}O_4N_2S$. The preparation lutenurine, possessing protistocidal and antimicrobial activity has been created on the basis of this alkaloid.

It was shown that nuphleine contains two furan rings and two hydroxy groups present in the α positions to nitrogen atoms. The reduction of nuphleine with sodium tetrahydroborate gave a quantitative yield of thiobinupharidine, for which structure (I) has recently been established [4, 5].

We give the results of a spectroscopic study of nuphleine which permits structure (II) to be ascribed to it.



I

II

The thiobinupharidine molecule (I) has six carbon atoms in α positions to nitrogen atoms: 4, 4', 6, 6', 10, and 10'. In the NMR spectrum of nuphleine there are two one-proton singlets the half width of which change on the addition of D_2O (Table 1); these signals must be assigned to protons geminal to hydroxy groups.

Thus, positions 4 and 4', and 10 and 10', are excluded for the hydroxy groups and only positions 6 and 6' remain possible.

The NMR spectra also confirmed the equatorial orientation of the β-furyl groups (trans-diaxial coupling constants 8.0 and 8.5 Hz for the protons at C_4 and $C_{4'}$) and of the methyl groups at C_1 and $C_{1'}$ (upfield shift of the signals of these groups by 0.17 ppm on passing from $CDCl_3$ to C_6D_6 [5]).

One of the hydroxy groups forms an intramolecular hydrogen bond and the other is free; in the IR spectrum of a dilute solution of nuphleine in CCl_4 (0.001 M) there are two bands in the region of stretching vibrations of OH bonds – a narrow one at 3628 cm^{-1} and a broadened one at 3535 cm^{-1}. This is also shown by the NMR results – one of the HC–OH signals is broadened ($W_{1/2}$ 5.0 Hz) as the result of hindrance to exchange; on the addition of D_2O the signal narrows (see Table 1). A consideration of a model shows that the formation of an intramolecular hydrogen bond is impossible only for an axial OH group at $C_{6'}$. In the case of an equa-

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