

Literature information on dimeric alkaloids of the tropane series is generalized.

Dimeric tropane alkaloids form a small group of natural compounds the structural basis of which consists of two tropane nuclei and one, two, or three fragments of, most frequently, a dibasic acid. The first representatives of this group were discovered as early as the last century [1]. Since this time, publications have appeared periodically on dimeric tropane alkaloids, which now number more than fifteen. However, there is no generalized material on this question in the literature available to us.

Dimeric tropane alkaloids, like the monomeric ones, are found in plants of the families Solanaceae, Erythroxylaceae, Convolvulaceae, and others. It must be mentioned that a definite type of dimeric tropane alkaloids is characteristic for certain plant species. In the generalization of information of structural investigations of dimeric tropane alkaloids, attention is attracted by the fact that different combinations of a known nitrogen-containing ring widely distributed in plants and an acid fragment lead to a multiplicity of types of structures of the tropane alkaloids. Common structural elements of all the dimeric tropane alkaloids are a tropane nucleus mono- or disubstituted in the C-6, C-3 and C-2 positions.

For the group of alkaloids under consideration it is possible to single out a type of bimolecular bases (group A) in which the bond between the monomers is created by the esterification of two amino alcohols by the carboxy groups of dibasic acids. As the latter are most frequently found  $\alpha$ -truxillic,  $\beta$ -truxinic, itaconic, mesaconic, and  $\alpha$ - and  $\beta$ -isatropic acids.

It is particularly possible to single out a group of alkaloids in which the bond between the monomers is formed in a different manner (group B), namely: dimerization takes place through the appearance of bond between the nitrogen atoms of heterocyclic nortropane nuclei through a  $-\text{CH}_2-\text{CH}_2-$  or  $>\text{C}=\text{O}$  bond.

The general principles for demonstrating the constitution of the dimeric alkaloids also follow from features of their structure. Thus, the main method for demonstrating the structures of the alkaloids of group A amounts to the hydrolytic cleavage of the dimolecular bases followed by the isolation and identification of the cleavage products from the amino alcohol fraction and the acid fraction of the hydrolysate. This leads to the isolation of the corresponding monomeric base — an amino alcohol, substituted at C-3, C-2, or C-6 — and a known acid, the identification of these substances causing no difficulties.

In the case of the alkaloids of group B, hydrolysis does not lead to the formation of a monomeric amino alcohol. A dimeric amino alcohol is obtained the structure of which is shown by spectroscopic methods.

With respect to the nature of the acid moieties, all the bimolecular alkaloids can be grouped in the following way:

- (I) truxillates (derivatives of truxillic acid);
- (II) isatropates (derivatives of  $\alpha$ - and  $\beta$ -isatropic acid);
- (III) veratrates (derivatives of veratric acid);
- (IV) derivatives of saturated aliphatic mono- and dibasic acids.

Let us pass to a consideration of individual groups of the dimeric alkaloids. The first information on the isolation of dimeric tropane alkaloids of group A appeared as early as the last century, when in 1887, the German scientist Hesse isolated  $\alpha$ - and  $\beta$ -truxillines from coca leaves [1]. The raw material of coca consists of two species of the genus Erythroxylon growing mainly in the western part of South America and more rarely in India, Africa, and

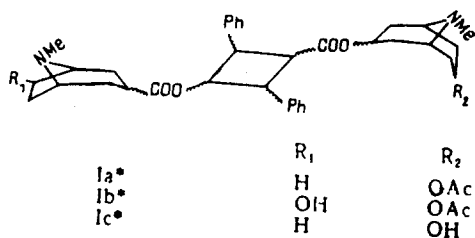
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Australia. The leaves of both species appear on the market: those from the Huanoco cocaine tree (*E. coca* L.) bear the name of Bolivian leaves or Huanuco leaves, and the others, obtained from the Trujillo cocaine tree (*E. truxillense* R.), are called Peruvian or Truxillo leaves. Both species of plant are cultivated in the island of Java.

$\alpha$ - and  $\beta$ -Truxillines are amorphous substances that have not been investigated in the pure form because of difficulties of separation.  $\alpha$ -Truxilline and  $\beta$ -truxilline which were originally named cocamine and isococamine, are optically active substances. On hydrolysis (heating with acids and alkalis) they break down with the formation of organic acids, an amino alcohol, and methanol. The two alkaloids give one and the same basic skeleton with the composition  $C_8H_{15}NO_3$ , called 1-ecgonine, and  $\alpha$ -truxillic and  $\beta$ -truxillic acids, respectively. The latter are dimers of cinnamic acid ( $C_{18}H_{16}O_4$ ) and are probably formed from it under the action of light.  $\alpha$ - and  $\beta$ -Truxillines have also been obtained synthetically from 1-ecgonine and  $\alpha$ -truxillic and  $\beta$ -truxillic acids, respectively, with subsequent methylation.

The plant *Erythroxyton hypericifolium* (a rich source of tropane alkaloids [4, 5]) is one of the five species of the section *Venelia* of the genus *Erythroxyton* that has been studied systematically. In comparison with other species, it contains a unique spectrum of alkaloids, including mixtures of tropane esters of acetic, phenylacetic, cinnamic, benzoic, and other, acids. In addition to 15 alkaloids, the majority of which are esters of cinnamic and benzoic acids, mixed cinnamoyl dimers have been isolated. The leaves, unlike the bark and the stems, contain heterodimers formed from the cinnamates in the leaves has also made possible the biosynthesis of dimeric alkaloids in the plant organism.



\* Stereochemistry not established.

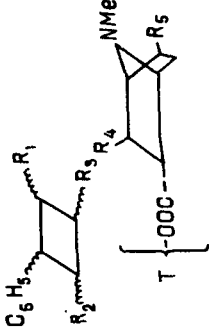
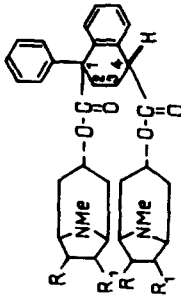
Three dimers with the general formula (I) have been identified: a dimer with a molecular mass of 600 ( $Ia$ ), an alkaloid with a molecular mass of 616 ( $Ib$ ), and a third dimer with a molecular mass of 558 ( $Ic$ ). The complete structures of the dimers have been established by a combination of chemical and spectral methods (mass spectrometry) [6, 7].

The alkaloid with a molecular mass of 600, having the composition  $C_{36}H_{44}N_2O_6$ , on hydrolysis gives acid and basic fractions. An acid with a molecular mass of 296 obtained on the hydrolysis of ( $Ia$ ) forms on mass spectrometry a fragment corresponding to truxillic acid. The peak of an ion with  $m/z$  180 that is characteristic for truxinic acid is not observed in the spectrum. The basic fraction contains two products: tropan-3-ol ( $M^+$  141) and tropane-3,6-diol ( $M^+$  157) formed on saponification of an acetyl group. It is more likely that compound ( $Ia$ ) is tropan-3-yl truxillate than the tropan-6-yl ester, as follows from its mass spectrum.

In view of the fact that in the mass spectra of the tropane alkaloids the main direction of fragmentation is the  $\alpha$ -cleavage of the heterocyclic ring with subsequent elimination of ethylene (if C-6 and C-7 are unsubstituted), the cleavage of the 1-7 bond (equivalent to the 5-6 bond) of ( $Ia$ ) leads to the loss by the molecular ion of a fragment corresponding in mass to splitting out of a  $-CH_2-CH-O-COCH_3$  group attached to C-6. In the case of tropan-3-yl truxillate, an ethylene molecule would be lost, which is not observed, and therefore ( $Ia$ ) is 6-acetoxytropan-3-yl truxillate.

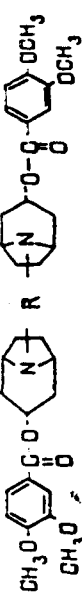
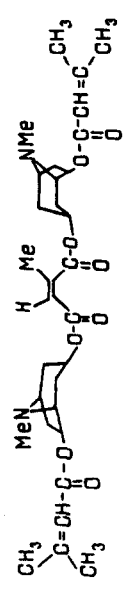
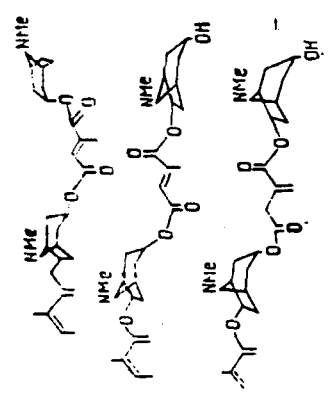
For the alkaloid with a molecular mass of 616, which has been isolated in the form of the picrate, the mass spectrum showed the loss by the molecular ion of the dimer of the fragments  $C(7)H_2C(6)HOCOCH_3$  and  $C(7)H_2C(6)HOH$ . No ions with  $m/z$  above 400 were detected in the mass spectrum, but with other mass-spectrometric methods (PAV) it was easy to detect the  $(M+1)^+$  ions and the components of cinnamates. On the basis of these facts, compound ( $Ib$ ) is a hydroxy derivative of ( $Ia$ ).

TABLE 1. Dimeric Tropane Alkaloids

Alkaloid	Composition	Plant	Structure
1	2	3	4
1, $\alpha$ -Truxilline	$C_{33}H_{48}N_2O_8$	Erythroxylon coca	
2, $\beta$ -Truxilline	$C_{34}H_{48}N_2O_8$		
3, 6-Acetoxytropan-3-yl tropan-3-yl truxillate	$C_{36}H_{44}N_2O_8$	Erythroxylon hypericifolium	
4, 6-Acetoxytropan-3-yl 6-hydroxytropan-3-yl truxillate	$C_{38}H_{44}N_2O_7$		
5, 6-Hydroxytropan-3-yl propan-3-yl truxillate	$C_{31}H_{44}N_2O_8$		
6. $\alpha$ -Belladonnine	$C_{31}H_{42}N_2O_4$	Physochlaina alata E. Korot.	

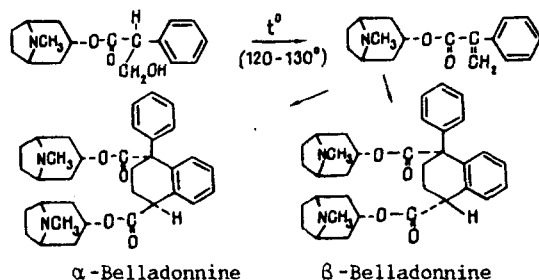
- 1:  $R_1 = R_2 = T$  ( $R_1 = -COOCH_3$ ;  $R_2 = H$ );  $R_3 = C_6H_5$   
 2:  $R_1 = R_2 = T$  ( $R_1 = COOCH_3$ ;  $R_2 = H$ );  $R_3 = C_6H_5$   
 3:  $R_1 = T$  ( $R_1 = H$ ;  $R_2 = OAc$ );  $R_3 = T$  ( $R_3 = R_4 = H$ );  $R_5 = C_6H_5$   
 4:  $R_1 = T$  ( $R_1 = H$ ;  $R_2 = OAc$ );  $R_3 = T$  ( $R_3 = H$ ;  $R_4 = OH$ );  $R_5 = C_6H_5$   
 5:  $R_1 = T$  ( $R_1 = H$ ;  $R_2 = OH$ );  $R_3 = T$  ( $R_3 = R_4 = H$ );  $R_5 = C_6H_5$

TABLE 1 Continued

1	2	3	4
7. $\beta$ -Belladonnine 8. $\alpha$ -Scopodonnine 9. $\beta$ -Scopodonnine 10. Subhirsine	$C_{28}H_{42}N_2O_4$ $C_{31}H_{46}N_2O_5$ $C_{34}H_{50}N_2O_6$ $C_{33}H_{48}N_2O_6$	• • • • Convolvulus sub- hirsutum	 <p>7: R = R<sub>1</sub> = H; 4<math>\beta</math>H 8: R + P<sub>1</sub> = &gt;O; 4<math>\alpha</math>H 9: R + R<sub>1</sub> = &gt;O; 4<math>\beta</math>H</p>
11. Convolvidine 12. Schizanthine B	$C_{31}H_{44}N_2O_6$ $C_{31}H_{44}N_2O_6$	Schizanthus pin- natus	 <p>10: R = &gt;C=O 11: R = -CH<sub>2</sub>-CH<sub>2</sub>-</p>
13. Schizanthine C 14. schizanthine D 15. Schizanthine D	$C_{28}H_{38}N_2O_7$ $C_{28}H_{38}N_2O_7$ $C_{28}H_{38}N_2O_7$	Schizanthus gra- hamii	

The third dimer, with a molecular mass of 558, is, as shown by the results of a comparative study of the mass spectra of (Ia) and (Ic), the product of the partial saponification of (Ia), and (Ic) is proposed for it.

In 1973, a number of alkaloids of the tropane series were isolated from Physochlaina alaica E. Korot. In addition to these, two minor dimeric alkaloids -  $\alpha$ - and  $\beta$ -belladonnines were isolated from the plant; these were known as synthetic compounds [8, 9] obtained from hyoscyamine by the scheme given below:

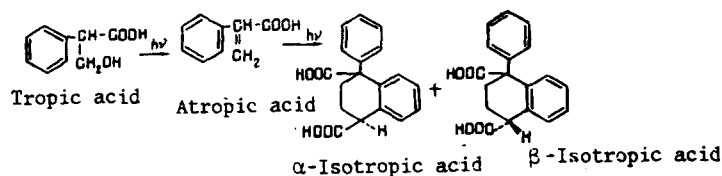


The isolation of  $\alpha$ - and  $\beta$ -belladonnines from the plant [10] indicates that an analogous reaction (possibly a photoreaction) probably takes place in the plant organism itself, but under milder conditions. Each of two alkaloids contains in the structure of its nucleus a monosubstituted tropane, and they are esters of tropine and  $\alpha$ - and  $\beta$ -isatropic acids. The molecular masses of the alkaloids correspond to that of a dimer of an apotropine. Their mass spectra revealed the presence in each case of the peak of a doubly-charged ion with  $m/z$  271 corresponding to the molecular ion of apotropine, which confirms the dimeric nature of the alkaloids. The PMR spectra of both alkaloids agree well with the proposed structure (chemical shifts,  $\delta$  scale, ppm):

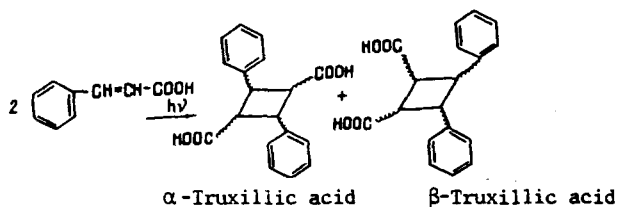
Alkaloid	NCH <sub>3</sub>	NCH <sub>3</sub> '	C <sub>3</sub>	C <sub>3</sub> '	C <sub>1,1'</sub> C <sub>5,5'</sub>	C <sub>2,2',4,4'</sub> C <sub>6,6',7,7'</sub>	C-H	Ar
$\alpha$ -Belladonnine	2,04 s	2,10 s	4,87 m	4,97 m	2,81 1	1,1-1,99 m	3,70 m	7,1(9H) s
$\beta$ -Belladonnine	2,06 s	2,12 s	4,92 m	5,02 m	2,84 q	1,1-2,01 m	3,65 m	7,09(7H) s 6,85(2H) q

In a similar manner to the formation of the belladonnines from an alkaloid of the scopolamine series, 1-hyoscyen, two products have been obtained by the dimerization of aposcopolamine, one of which, called scopodonnine by analogy with  $\beta$ -belladonnine, was ascribed the structure of  $\beta$ -scopodonnine. The second product was poorly characterized. In all probability it was an isomer of  $\beta$ -scopodonnine, i.e.,  $\alpha$ -scopodonnine (Table 1).

As can be seen from their structures, the formation of the dimeric tropane alkaloids takes place through the dimerization of acids. Thus, in the formation of the alkaloids belladonnines and scopodonnines tropic acid undergoes dimerization, under certain conditions (under the action of light) being converted in the plant organism into isotropic acid (dimer). It may be assumed that this is a case of a natural photoreaction.



The formation of truxillic acid from cinnamic acid takes place analogously:



The acids formed as the result of the dimerization are optically active compounds ( $\alpha$ - and  $\beta$ -isotropic and  $\alpha$ -truxillic and  $\beta$ -truxinic acids) and, accordingly, form with amino alcohols two series of optically active alkaloids ( $\alpha$ - and  $\beta$ -belladonnines,  $\alpha$ - and  $\beta$ -scopodonnines,  $\alpha$ -truxillines, and  $\beta$ -isotruxillines).

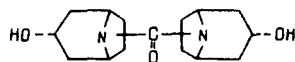
In the dimeric alkaloids of some plants of the family Convolvulaceae (subhirsine, convolvuline), dimerization takes place through the linkage of two amino alcohol residues (the alkaloids of groups C).

In a study of the alkaloids of the roots of Convolvulus subhirsutus Rgl., in addition to the five known bases of the tropane series two alkaloids of dimeric nature were isolated - subhirsine [12] and convolvidine [13]. They are both diesters of veratric acid and the amino alcohol nortropine.

The structures of the two alkaloids were established on the basis of a number of chemical reactions and of the spectral characteristics of the alkaloids themselves and the products of their chemical transformations.

The mass spectrum of subhirsine contains the peak of the molecular ion with  $m/z$  608 and the peak of a doubly charged ion with  $m/z$  304 corresponding to the molecular mass of the monomer convolvamine, which shows that subhirsine consists of two structural units of convolvine.

The presence of the band of an amide carbonyl group in the IR spectrum of subhirsine indicates the nature of the linkage of the two equivalent halves of convolvine through nitrogen atoms by means of a carbonyl group. After alkaline hydrolysis, from the acid fraction of the hydrolysate an acid was isolated which was identified as veratric acid, and the amino alcohol fraction yielded a substance with mp 260°C and a molecular mass of 280 the spectral characteristics of which corresponded to structure (II):



On the basis of these facts, subhirsine is represented by the structure given in Table 1, which agrees well with its properties.

The dimeric alkaloid convolvidine is analogous in structure to subhirsine (see Table 1). It is also a diester of veratric acid and the amino alcohol nortropine. The difference consists in the nature of the bond between the two symmetrical halves of convolvine. In this case, the bond is made between the nitrogen atoms through a  $-\text{CH}_2-\text{CH}_2-$  link. It must be mentioned that all the alkaloids isolated from this plant are esters of veratric acid and a substituted nortropine amino alcohol, the position of substitution being the nitrogen atom. This apparently also determines the individuality of the species. Such a characteristic feature is also observed in the case of alkaloids of other plants.

Plants of the genus Schizanthus have also proved to be a rich source of dimeric alkaloids, but of a somewhat different type; namely, the acid moieties of this group of alkaloids consist of angelic, itaconic and mesaconic acid linked in different ways. The isolation of tropane alkaloids from parts of this genus is a chemotaxonomic characteristic of the genus Schizanthus. A parallel is drawn between the specific botanical characteristics of Schizanthus and the structural type of the alkaloids contained in it.

Schizanthus pinnatus plants [14] have yielded the dimeric alkaloid schizanthine B - a complex tropanol diester of senecionic acid. Thus, absorption in the IR spectrum ( $1723, 1645 \text{ cm}^{-1}$ ) shows the presence of an  $\alpha, \beta$ -unsaturated acid, while the intensity of the UV spectrum indicates the presence of three such groups. The mass spectrum indicates the presence in the structure of schizanthine B of two senecionic acid residues and shows the 3,6-diacyloxypitropane structure of schizanthine B.

From another species, Schizanthus grahamii [15], in addition to known alkaloids, three dimeric alkaloids have been isolated which have been called schizanthines C, D, and E. They are tropanol diesters of mesaconic and itaconic acids (see Table 1).

The structures of these compounds were established on the basis of chemical transformations and spectral characteristics. Their PMR spectra give a large amount of information.

Diagnostic are the chemical shifts and multiplicities of olefinic protons, and also the positions and multiplicities of the skeletal protons at the point of attachment of the ester fragment to the tropane nucleus. Thus, signals at 6.82, 6.74, and 6.72 ppm in schizanthines B, C, and D, respectively, show the presence of mesaconic acid residue, while a multiplet with its center at 6.04 ppm indicates the presence in schizanthines C and D of angelic acid residues. On the other hand, a triplet at  $\delta$  5.09 ppm with an intensity of two proton units shows that schizanthine C contains two tropane units linked with an ester group through C-3, while the attachment of a third ester residue at C-6 follows from the presence of a characteristic multiplet (dd) at  $\delta$  5.48. The mass spectrometric fragmentation of schizanthine C is characteristic for 3,6-diacetyloxypitropine derivatives, while the relative intensities of the peaks of ions with  $m/z$  238, 222, 138, and 122 shows the presence of an angelic acid residue at C-6. Schizanthine D differs from schizanthine C by one oxygen atom, as follows from the mass spectrum, which shows that an angelic acid residue is attached to one of the tropane units at C-6, while a triplet at 4.06 ppm in the PMR spectrum of schizanthine D shows that there is a free OH group at C-3. This is also confirmed by the intense peak of an ion with  $m/z$  113, absent from the spectrum of schizanthine C. Signals at  $\delta$  5.69 ppm (H-6), 5.46 ppm (H-6), and 5.08 ppm (H-3) and their multiplicities show the nature of the substitution in this alkaloid.

Schizanthine E is isomeric with schizanthine D. The main distinction consists in different positions of the singlets, namely: at 6.30, 5.72 (1 H each), and 3.31 (2 H), which shows the presence of an itaconic in place of a mesaconic acid residue.

The hydrolysis of all four dimeric alkaloids leads to (+)-(3R, 6R)-tropane-3 $\alpha$ ,6 $\beta$ -diol, which determines their absolute configuration (see Table 1).

The biogenetic pathway for the formation of the dimeric tropane alkaloids can be represented as a photochemical reaction taking place in the native plant organism, apparently, under the influence of various factors (temperature, illumination, action of enzymes). It can be stated that the photochemical reaction is a common and unique method of obtaining compounds of very diverse structures.

The biological activities of the dimeric tropane alkaloids have scarcely been studied. It is known only that quaternary halogen derivatives of the belladonnines possess a curare-like action. The search for alkaloids of dimeric nature is therefore promising, since it opens up a route to the finding of new types of structures of alkaloids with different pharmacological activities, enriching the chemistry of natural and physiologically active compounds.

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