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THE TECHNOLOGICAL CLASSIFICATION OF ALKALOIDS AND METHODS OF OBTAINING THEM FROM PLANTS

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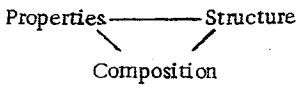
UDC 547.94+615.45+615.32

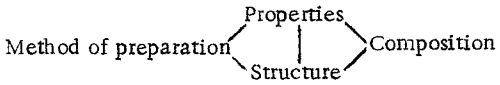
About 100 individual alkaloids are produced on the industrial scale [1]. In spite of this, there is no acceptable classification and systematization of the technology of the alkaloids that would lead to a generalization of all the experience accumulated in this field. In our opinion, this situation is due to the fact that insufficient attention has been devoted to the connection of the method of obtaining alkaloids with their structure, composition, and properties.

Academician B. M. Kedrov, generalizing methodological questions of chemistry, has put forward the scheme



[2], in which chemical technology does not have its due reflection. At the same time, from hydrogen to kurchatovium, from methane to protein, in all cases the method of preparation depends on the composition, structure, and properties. It is impossible to find even one example where the above-mentioned parameters of the compound being isolated has not been taken into account in technology.

On the basis of literature information and our own experiments on the development of a technology for producing the alkaloids of *Vinca erecta* we consider the following scheme to be the most correct:



since as the properties, composition, and structure of a substance become known so is the method for its preparation developed.

In order to find a parameter which to some extent would give a quantitative characterization of the main properties of an alkaloid and at the same time would be accessible to direct measurement, we have begun the study of the behavior of alkaloids in heterogeneous systems consisting of chloroform and buffer solutions, since the main processes of alkaloid technology do in fact involve heterogeneous systems: extraction, sorption, liquid–liquid extraction, etc. [3].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 743-753, November-December, 1977. Original article submitted May 24, 1977.

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Distribution of Alkaloids in a Heterogeneous System

In the distribution of the combined alkaloids of *V. erecta* between chloroform and buffer solutions (BS's) it was found that there is a sequence of transition of a number of the main alkaloids that is repeated in all experiments [4]:

Akaloid [1]	pH of Passage into the Buffer
Tombozine	5,5–6,0
Vincanidine	5,0–5,5
Akuammidine	4,5–5,0
Vincarine	3,5–4,5
Vincanine	3,0–3,5
Vincamine	2,0–3,0
Ervamine	10% H_2SO_4

Assuming that the sequence of passage into buffers should correspond to the arrangement of the alkaloids according to the values of their dissociation constants, we determined the ionization constants pK_a of the same alkaloids by the potentiometric method [5].

Alkaloid	pK_a in 20% Methanol	pK_a in Chloroform
Tombozine	7,54	6,30
Vincanidine	6,84	5,91
Akuammidine	6,66	5,15
Vincarine	6,91	5,75
Vincanine	7,79	5,72
Vincamine	6,62	5,81

In view of the absence of a clear relationship between the pH values of transition and the pK_a values in water, we determined the pK_a values in chloroform — the phase in equilibrium with the aqueous layer of the heterogeneous system [6]. It is not difficult to see that the relationship between the pH of transition and the pK_a value of the substance undergoing partition has a fairly complex nature both in water and in chloroform.

The same can be said concerning the main opium alkaloids, the pK_a and transition pH values of which are known from the literature:

Alkaloid	Optimum pH of the Buffer [7]	pK_a *[8]*
Morphine	6,2	7,87
Codeine	4,6	7,90
Thebaine	1,0	7,00
Narcotine	<0,6	5,80
Papaverine	<0,6	5,90

The complexity of finding the relationship $pK_a = f$ (pH of transition) is also due to the fact that the pH value for the transition of an alkaloid is determined not only by its basicity but also by its solubility in the two phases of the heterogeneous system and depends on the properties of the heterogeneous system, etc. Furthermore, the pK_a value is determined in a homogeneous system and the distribution in a heterogeneous system.

In considering this question, we have undertaken a more detailed investigation of the behavior of alkaloids (with, as examples, the bases of *V. erecta* and others) in chloroform–buffer solutions systems under various conditions [9]. It was established by special experiments that in all cases the distribution process takes place by pure salt formation. The main criterion of partition is the partition coefficient K, defined by the formula

$$K = \frac{C_{BS}}{C_{chl}} .$$

Below we give the partition coefficients of some alkaloids in chloroform–buffer solution systems:

pH	Vincamine	Vincanine	Vincarine	Akuammidine	Vincanidine	Tombozine
8,0	0	0	0	0	0	0
7,5	0	0	0	0	0	0
7,0	0	0	0	0	0,07	0,3
6,5	0	0	0	0	0,36	0,5
6,0	0	0,062	0	0,14	0,50	1,3
5,5	0	0,13	0,2	0,80	2,0	5,0
5,0	0,007	0,17	0,6	1,30	8,80	17,0
4,5	0,18	0,35	3,1	2,60	29,0	+
4,0	0,41	0,59	5,3	5,0	+	+
3,5	0,76	1,2	17,0	23,0	+	+
3,0	2,14	12,0	+	+	+	+
2,5	6,05	33,0	+	+	+	+
2,0	13,1	+	+	+	+	+

Thus, the partition coefficients of the alkaloids vary within wide limits as functions of the pH of the buffer solution.

To compare the partition results, we made use of the value of the pH of the buffer solution extracting just half the amount of a base from the equilibrium organic phase, i.e., the value of the pH at K = 1. This value, which is denoted by $pH_{1/2}$, is determined from a plot of the relationship $K = f(pH)$ (Fig. 1).

From the information given above we determined the $pH_{1/2}$ value for each alkaloid similarly:

$pH_{1/2}$ from Chloroform	Base	pK_a
6,35	Tombozine	7,54
5,80	Vincanidine	6,84
5,35	Akuammidine	6,66
4,90	Vincarine	6,91
3,60	Vincanine	7,79
3,30	Vincamine	6,62

The sequence of the alkaloids according to their $pH_{1/2}$ values coincides with the sequence of extraction of the same alkaloids in the partition of the combined alkaloids, but it does not coincide with their pK_a values. The same thing can be said about the main opium alkaloids:

$pH_{1/2}$	Alkaloid	pK_a
>9,0	Morphine	7,87
5,80	Codeine	7,95
3,80	Thebaine	7,00
<1,5	Papaverine	5,90
<1,5	Narcotine	6,18

It is known from the literature that "...under the influence of nonaqueous solvents not only does the strength of bases (pK_a) change but also the ratio of their strengths" [8]. To evaluate the influence of a change in the organic phase of the value of $pH_{1/2}$ we have performed similar investigations in benzene–buffer solution systems as well [9]:

Alkaloid	$pH_{1/2}$ chl	$pH_{1/2}$ benzene	$\Delta pH_{1/2}$
Tombozine	6,35	7,50	1,15
Vincanidine	5,80	7,10	1,30
Akuammidine	5,35	6,30	0,95
Vincarine	4,90	6,30	1,40
Vincanine	3,60	5,70	2,10
Vincamine	3,30	4,60	1,30

As the results given show, in benzene–buffer solution heterogeneous systems the magnitude of $\Delta pH_{1/2}$ rises from 0.95 to 2.10 with no change in the sequence relative to the chloroform system [10].

Although the value of $pH_{1/2}$ depends on many factors, one of the determining factors is the basicity of the alkaloid, and therefore a differentiation of the basicity of alkaloids according to the $pH_{1/2}$ values may be extremely useful for technological purposes. It must be

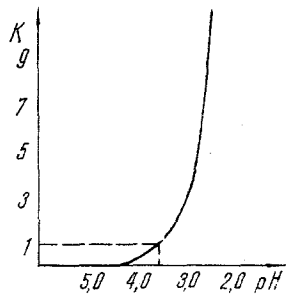


Fig. 1. Partition curve of vincanine.

mentioned that constants analogous to $pH_{1/2}$ are used in the chemistry and technology of complex compounds [11] and also for determining "the true partition coefficients of a number of tropane alkaloids" [12].

Investigations of the partition of various alkaloids forming drug preparations between buffer solutions and chloroform are performed on a fairly large scale. We have determined the following $pH_{1/2}$ values on the basis of literature information:

Alkaloid	$pH_{1,2}$ chl	Literature
Coniine	9,25	13
Narceine	>8,0	14
Securinine	>8,0	15,16
Cocaine	>8,0	17
Anabasine	8,0	18
Ethylmorphine	8,0	19
Norhyoscyamine	7,80	12
Pilocarpine	7,85	20
Normicotine	7,63	12
Atropine	7,4	21
Hyoscyamine	7,00	12
Valeroidine	6,67	12
Mellictine	6,00	22
Scopolamine	5,90	23
Nicotine	5,75	12,24
Trichodesmine	5,50	25
Hyoscyine	5,48	12
Galanthamine	5,15	26
Tigloidine	5,08	12
Apoatropine	4,65	12
Colchamine	4,00	27
Thebaine	3,80	28
Theophylline	2,75	29
Papaverine	<1,6	30
Colchicine	<1,5	31
Caffeine	<1,4	32
Narcotine	<1,0	33

The Connection of the R_f Values of Alkaloids with Their $pH_{1/2}$ Values

One of the widely used heterophase processes is thin-layer chromatography (TLC) [44]. The question of the existence of a correlation between the $pH_{1/2\,chl}$ and the R_f values (in the chloroform–methanol (9:1) system; the R_f values were determined [34] in a thin layer of LS 5/40 μm silica gel and Silufol) is of interest:

Alkaloid	$pH_{1,2}$ chl	$Rf \pm 0,02$	
		LS 5/40 μm	Silufol
	Opium Alkaloids		
Morphine	>9,0	0,07	0,11
Codeine	5,80	0,23	0,26
Thebaine	3,80	0,49	0,39
Papaverine	>1,6	0,83	0,96
Narcotine	>1,0	0,88	0,96
	Isoquinoline Alkaloids		
Salsoline	8,15	0,06	0,05
Salsolidine	6,20	0,13	0,16

Indole Alkaloids			
Tombozine	6,35	0,16	0,19
Vincanidine	5,80	0,20	0,26
Akuammidine	5,35	0,40	0,35
Vincarine	4,90	0,46	0,37
Vincanine	3,60	0,50	0,43
Vincamine	3,30	0,53	0,71

With a fall in $pH_{1/2}$ the value of R_f rises for all the alkaloids but it still does not appear possible to derive a definite mathematical relation $pH_{1/2} = f(R_f)$. A similar correlation is observed in a comparison of the values of $pH_{1/2}$ benzene with R_f values in the benzene–methanol (9:1) system [34].

The Partition of Some Alkaloids between Water and Chloroform

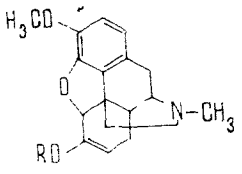
To investigate the possibility of the partition of alkaloids in a weakly dissociated form (in the form of the bases) the partition of a number of alkaloids between water (distilled) and chloroform has been studied. The values of the partition coefficients ($K_{base} = C_{water}/C_{chl}$) were compared with the $pH_{1/2}$ values and the R_f values on TLC. The alkaloids were determined qualitatively with a 1% solution of cerium ammonium sulfate in concentrated sulfuric acid [35], Dragendorff's reagent, and tungstosilicic acid.

As the experimental results show, a definite relationship exists between R_f, K_{base}, and $pH_{1/2}$; the smaller the value of R_f and the larger the value of $pH_{1/2}$ the better are the alkaloids extracted by water from chloroform solution in the form of bases. The phenolic bases morphine, salsoline, and vincanidine have relatively high values of K_{base}, which is apparently due to the hydrophilicity of the phenolic hydroxy group. Alkaloids with $R_f > 0.45$ are extracted extremely feebly by water from chloroform solution. Alkaloids are distributed between water and chloroform in the following way:

Alkaloid	$pH_{1/2}$	K_{base}	R_f
Opium Alkaloids			
Morphine	>9,0	7,00	0,07
Codeine	5,80	0,20	0,26
Thebaine	3,80	0,00	0,39
Papaverine	<1,6	0,00	0,96
Narcotine	<1,6	0,00	0,96
Isoquinoline Alkaloids			
Salsoline	8,15	0,60	0,06
Salsolidine	6,20	0,13	0,13
Indole Alkaloids			
Tombozine	6,35	0,50	0,16
Vincanidine	5,80	1,00	0,20
Akuammidine	5,35	0,33	0,40
Vincarine	4,90	0,00	0,46
Vincanine	3,60	0,00	0,50
Vincamine	3,30	0,00	0,53

The Connection between the $pH_{1/2}$ and R_f Values of an Alkaloid and Its Structure

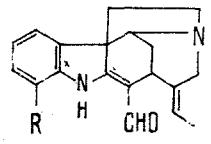
Among the compounds that we have investigated there are bases similar in structure [1, 36] such as codeine–thebaine, vincanidine–vincanine, and salsoline–salsolidine, and a number of alkaloids and their nor derivatives. It was of interest to compare these substances with respect to their R_f, $pH_{1/2}$, and pK_a values.



1

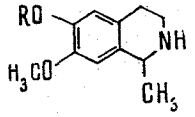
Codeine: $R = H$, $pH_{1/2} = 5,8$, $R_f = 0.23$

Thebaine: $R = CH_3$, $pH_{1/2} = 3,8$, $R_f = 0.49$

2 

Vincanidine: $R = OH$, $pH_{1/2} = 5,8$ $R_f = 0.20$

Vincanine: $R = H$, $pH_{1/2} = 3,6$, $R_f = 0.50$

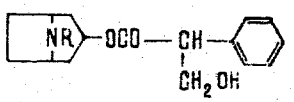
3 

Salsoline: $R = H$, $pH_{1/2} = 8,15$, $R_f = 0.06$

Salsolidine: $R = CH_3$ $pH_{1/2} = 6,15$, $R_f = 0.13$

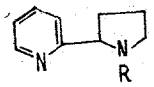
Thus, the presence of a —OH functional group causes an increase in the $pH_{1/2}$ value by approximately two units and a decrease in R_f.

It must be observed that in a number of alkaloids the $pH_{1/2}$ value is less than that of the corresponding nor bases.

1 

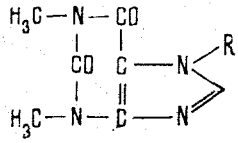
Norhyoscyamine: $R = H$, $pH_{1/2} = 7.89$

Hyoscyamine: $R = CH_3$, $pH_{1/2} = 7.00$

2 

Nornicotine: $R = H$, $pH_{1/2} = 7.63$

Nicotine: $R = CH_3$, $pH_{1/2} = 6.00$

3 

Theophylline: $R = H$, $pH_{1/2} = 2.75$

Caffeine: $R = CH_3$, $pH_{1/2} = 1.5$

These examples give grounds for concluding that the functional groups of an alkaloid have a considerable influence on its $pH_{1/2}$ value.

Technological Classification of Alkaloids

The facts given above confirm that it is possible to use the $pH_{1/2}$ value as a technological parameter characterizing the heterophase processes of alkaloid technology.

According to their technological characteristics, alkaloids can be provisionally grouped in the following way:

Strong Bases. These can be extracted from chloroform solution with water and buffer solutions having pH > 7. The majority of them are quaternary and phenolic alkaloids which are well sorbed onto molecular and ion-exchange sorbents but are poorly eluted. They have the following constants:

$$9.0 < pH_{1/2\,chl}; \quad 0 \leqslant R_{f\,chl} < 0.1;$$

Bases of Medium Strength. These pass satisfactorily from chloroform into a buffer solution and from an aqueous solution (after alkalinification) into chloroform. They are sorbed and desorbed fairly well:

$$1.5 \leqslant pH_{1/2\,chl} \leqslant 9.0; \quad 0.1 \leqslant R_{f\,chl} \leqslant 0.80;$$

Weak Bases. These are not extracted from chloroform by water. They are extracted poorly or not at all from chloroform by buffer solutions and even by 10% H_2SO_4 solution. They are

poorly sorbed and are almost always eluted with the first fraction of the eluate:

$$pH_{1/2\,chl} \leqslant 1.5;\ R_{f\,chl} \geqslant 0.80.$$

In our opinion, this classification is convenient, takes many physicochemical properties of the alkaloids into account, permits their isolation and separation to be carried out purposefully, and makes classifications proposed previously [37-43] more concrete.

Let us consider methods for obtaining alkaloids with different basicities and attempt to elucidate the differences between them. Since several methods of preparation exist for many alkaloids, we have dwelt mainly on the industrial method, which is the most rational and economic and, consequently, takes into account more fully the physicochemical characteristics of the substance. Laboratory methods are subordinate only to the aim of the maximum isolation of the total alkaloids and are not restricted by the discarding of a cheap solvent or by technical safety, etc. For a number of bases the $pH_{1/2}$ values are unknown, and therefore we have used the R_f values of the alkaloids on TLC in chloroform–methanol and chloroform–ethanol systems.

Strongly Basic Alkaloids. Methods of obtaining the alkaloids given below have been studied:

Alkaloid	R_f [44, 45]	Literature
Morphine	0,03	46
Ergometrine	0,00	47, 48
Arecoline	0,00	49, 50
Berberine	0,00	49–51
Sparteine	0,00	49
Spherophysine	0,00	52, 53
Tubocurarine	0,00	49
Muscarine	0,00	54

A feature of the technology for the production of strongly basic alkaloids is the absence of a liquid–liquid extraction (LLE) process: in the production of d-tubocurarine, spherophysine, berberine, and muscarine there is no such process at all, and in the isolation of arecoline and sparteine it is used once and, moreover, from concentrated solutions of these alkaloids; for morphine and ergometrine a sorption process is used with desorption carried out at a high temperature. The main cause of the limited use of LLE in the technology of the strongly basic acids is the better solubility of the bases in water than in organic solvents.

In almost all methods the extractant used for obtaining the alkaloids from the plant raw material is water, aqueous solutions of acids, or alcohols, which readily extract them from the raw material.

Alkaloids of Medium Basicity. The technologies of the production of the following bases have been considered:

Alkaloid	R_f [44, 45]	Literature
Pilocarpine	0,32	49
Yohimbine	0,33	49,50
Ephedrine	0,36	59
Emetine	0,38	49
Scopolamine	0,46	49,58
Vincamine	0,53	55
Lobeline	0,55	49,57
Strychnine	0,57	49,50
Eserine	0,59	49,50
Reserpine	0,63	56

Characteristic for the alkaloids of medium basicity is the possibility of using within wide limits the values of the partition coefficients as functions of the pH, which frequently permits the use of LLE in the development of the technology of obtaining the bases of this group.

These bases can be extracted from the plant both by organic solvents (after the plant

has been moistened with solutions of ammonia or caustic soda) and by aqueous solutions of acids.

It is striking that from the chemical point of view the group of alkaloids of medium basicity has been studied most fully because of the relative ease of their isolation from the plant.

Weakly Basic Alkaloids. Industrial methods for obtaining a number of bases of this group have been described in the literature:

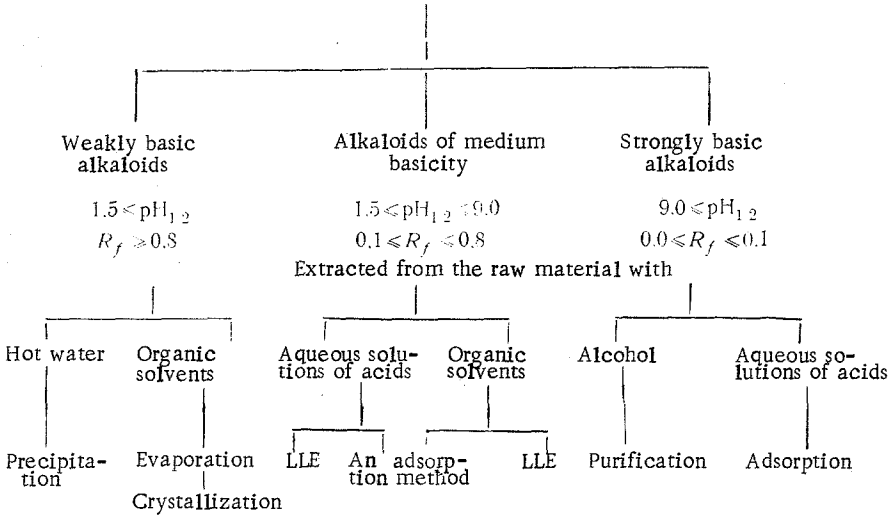
Alkaloid	R_f [44, 45]	Literature
Solasodine	—	60
Narcotine	0,81	36,59
Papaverine	0,85	36,59
Caffeine	—	59
Hydrastine	—	49
Colchicine	—	49

LLE is hardly used in the preparation of these alkaloids. They do not give salts that are stable in aqueous solutions, because of which they cannot be extracted completely from chloroform solution with aqueous solutions of acids, and they are poorly extracted from the plant by cold water and aqueous solutions of acids but are extracted better by organic solvents.

The existence of fairly distinct differences in the properties of the alkaloids as functions of their basicities, and also in industrial methods for their isolation enables us to consider that an acceptable classification of methods for obtaining the alkaloids is the following:

1) the technology of the strongly basic alkaloids;
2) the technology of the alkaloids of medium basicity; and
3) the technology of the weakly basic alkaloids.

This technological classification of methods for obtaining alkaloids is shown in generalized form below.



The Development of a Basic Technological Scheme for the Isolation of the Alkaloids of *V. erecta*

The hydrochlorides of vincanine, ervinine and vincamine — the main alkaloids of *V. erecta* — and also quaternary derivatives of vincanine and vincanidine have been approved by the Pharmacological Committee of the Ministry of Public Health of the USSR for use in medical practice. Thus, the necessity has arisen for developing a rational technological method for their production from this plant.

These alkaloids belong to the medium basicity group. According to the scheme given, three methods may be recommended for their production:

1) extraction of the raw material with organic solvents followed by reextraction with acid solutions, etc.;
2) extraction of the raw material with aqueous solutions of acids, sorption on ion-exchange resins, desorption, etc.; and
3) extraction of the raw material with aqueous solutions of acids with the subsequent use of LLE with organic solvents.

The first method has been developed previously [61, 62]. In our investigations we have confirmed the suitability of the use of the second and third methods in the production of these alkaloids [61-75].

We have checked the proposed classification and the basic ideas of this work in the development of a technology for the production of peganine hydrochloride from *Peganum harmala* [76-78] and in the performance of the polybuffer separation of complex mixtures of alkaloids from the plants *Vinca erecta* [4, 79], *Petilium raddeana* [80], *Buxus sempervirens* [81], *Peganum harmala* [82], and *Nitraria schoberi* [83].

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P A R T I A L M E T H Y L A T I O N O F C A R B O H Y D R A T E S

PARTIAL METHYLATION OF METHYL β-L-ARABINOPYRANOSIDE

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UDC 547.917+543.544.45

We have previously [1] studied the kinetics of the partial methylation of methyl β-L-arabinopyranoside by Purdie's method. We have now obtained information on the methylation of methyl β-L-arabinopyranoside by other methods.

As can be seen from Tables 1-3, in the initial stages of the partial methylation of methyl β-L-arabinopyranoside the 2-O-methyl ether predominates in the monomethyl ether fraction, and the amount of 3-O-methyl ether formed is greater than that of the 4-O-methyl ether.

It must be noted that in methylation by Kuhn's method in the presence of barium oxide the amount of 2,3-di-O-methyl ether rises sharply toward the end of the reaction (50.6% after 1.5 h), and this method is therefore suitable for the preparative production of the 2,3-di-O-methyl ether. The rate of methylation of methyl β-L-arabinoside by this method is considerably less than the rate of methylation of methyl β-D-xyloside [2]. The exhaustive methylation of the latter was complete in 1 h, while the conversion of methyl β-L-arabinoside into the fully methylated derivative was only 84% complete even after 2 h.

TABLE 1. Partial Methylation by Haworth's Method

Time, min	Initial arabinoside, %	Methyl ether, %					
		2	3	4	2,3	2,4+3,4	2,3,4
10	63,2	14,5	8,5	7,0	3,8	2,4	0,6
20	45,1	17,6	10,6	8,4	8,5	6,8	3,0
30	32,4	19,2	9,7	10,0	13,3	9,6	5,8
45	24,7	18,3	8,7	9,7	14,5	12,2	11,9
60	14,9	16,5	6,0	9,0	18,9	14,5	20,2
120	4,0	7,2	2,1	3,8	17,2	11,2	54,5

TABLE 2. Partial Methylation by Kuhn's Method (Ag_2O + CH_3I)

Time, min	Initial arabinoside, %	Methyl ether, %					
		2	3	4	2,3	2,4+3,4	2,3,4
10	78,3	9,8	7,8	4,1	—	—	—
20	67,3	10,9	12,9	6,5	1,2	1,2	—
30	43,7	21,2	17,9	9,6	2,5	5,7	—
45	25,5	21,6	25,7	13,2	4,6	9,1	0,3
60	13,7	18,9	35,1	11,4	10,4	9,8	0,7
90	1,6	12,7	35,5	8,2	20,1	18,6	3,3
120	—	11,7	19,8	7,9	15,5	17,0	13,1
180	—	—	7,6	3,0	36,7	15,6	37,1
240	—	—	6,1	2,2	33,5	14,8	43,4
480	—	—	2,1	1,1	25,8	10,6	60,4

Pacific Ocean Institute of Bioorganic Chemistry, Far Eastern Scientific Center of the Academy of Sciences of the USSR, Vladivostok. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 753-755, November-December, 1977. Original article submitted July 1, 1977.

 0009-3130/77/1306-0634$07.50