TROPOLONE ALKALOIDS

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The tropolone alkaloids – colchicine and its natural analogs and their precursors – have been widely studied in the last two decades. The interest of workers in them is due to the peculiar structure of these compounds, their strong influence on cell division, their value in polyploidy and cytology, and their use in the chemotherapy of malignant tumors and some other fields of biology and medicine. The present review gives information on the distribution of colchicine-containing plants, the tropolone alkaloids isolated from them, and the chemical transformations of these compounds.

Plants of the family Liliaceae containing colchicine and its associates grow mainly in Europe, Africa, and Western and Central Asia. Many of them have been investigated for the presence of alkaloids. At the present time, compounds of this class have been detected in 15 plant genera:

Genus	Growth Site	References
Androcymbium	Northern and Southern Africa	1–5
Anguillaria	Australia	5
Baeometra	Southern Africa	5
Bulbocodium	Central Europe	6,7
Camptorrhiza	Southern Africa	8
Colchicum	Western, central, and southern Europe, Asia Minor, central Asia, northern India, Iran, north Africa	1–3,6,8–32, 34–36
Dipidax	Southern Africa	5,6
Gloriosa	Tropical and southern Africa, India, China, Indochina	1–4,23,37–39
Iphigenia	Tropical Africa, India	6,8,40
Kreysigia	Australia	25,41,42,42a
Littonia	Africa	1–4,23,43
Merendera	Central and southern Europe, northern and Central Africa, Iran, Hindustan	1–3,8,10 21,25,33,34, 44–51
Ornithoglossum	Southern and equatorial Africa	4–6
Sandersonia	Southern Africa	1–4
Wurmbaea	Southern Africa	5

A review of the literature on the isolation of the tropolone alkaloids up to 1958 was included in a monograph by Prof. F. Šantavý [1] and there is also some additional information on this question in other reviews [52, 53].

The plant genera mentioned above are combined in Western European systematics into the subfamily Wurmbaeoideae [54, 55]; the presence of tropolone alkaloids is a taxonomic characteristic of the plants of this subfamily. According to the plant systematics adopted for the USSR, it corresponds to the subfamily Melanthioides [56].

It must be pointed out that in colchicine-containing plants, in addition to the tropolone alkaloids, their photochemical isomers are present. Characteristics of some plants is also the presence of tetrahydroisoquinoline and homomorphine bases [34, 55, 58-60].

According to the available information [61-64], the colchicine-containing plants in the USSR are represented by 11 genera: *Colchicum* L., *Merendera* Ramond. *Bulbocodium* L., *Anthericum* L., *Hemerocallis* L., *Ornithogalum* L., *Puschkinia* Adams, *Bellevalia* Lapeyrouse, *Lilium* L., *Tulipa* L., *Eremurus* Bieb. However, according to F. Šantavý [2] there are no colchicine alkaloids in plants of the genera *Ornithogalum* L., *Anthericum* L., *Tulipa* L., and *Hemerocalis* L. Tropolone compounds have been detected only by qualitative reactions in the genera *Puschkinia* Adams, *Bellevalia* Lapeyrouse, *Lilium* L., and *Eremurus* Bieb.

Thus, the presence of colchicine alkaloids has been reliably established in only three of the plant genera mentioned that grow in the USSR – *Colchicum* L., *Merendera* Ramond, and *Bulbocodium* L. *Colchicum* L. (autumn crocus) and *Merendera* Ramond (merendera) belong to the most highly alkaloid-bearing genera of the fam-

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TABLE 1

Alkaloid and its symbol	Composition	mp, °C	$[\alpha]_D$ in $CHCl_3$, deg	Year of isolation	Source of isolation and refererence
Colchicine, A	$C_{22}H_{25}O_6N$	155–157	–122	1819	Colchicum autumnale [1]
N-Formyldeacetylcochicine, B	$C_{21}H_{23}O_6N$	265–267	–167	1950	″ [1]
2-Demethylcolchicine, E	$C_{21}H_{23}O_6N$	178–180	–133	1950	″ [1]
3-Demethylcolchicine, C	$C_{21}H_{23}O_6N$	276–278	–263	1950	″ [1,22]
Colchamine, F	$C_{21}H_{25}O_5N$	184–186	–127	1950	″ [1]
2-Demethylcochamine, S	$C_{20}H_{23}O_5N$	136–138	–120	1952	″ [1]
Colchicoside	$C_{27}H_{33}O_{11}N$	216–218	–360	1952	″ [1]
Colchiceine	$C_{21}H_{23}O_6N$	175–177	–256	1953	″ [1]
3-Demethyl-N-deacetylcolchicine, U	$C_{19}H_{21}O_5N$	—	—	1953	″ [1]
Colchameine, Ta	$C_{20}H_{23}O_5N$	133–135	–211	1954	″ [1]
Speciosine	$C_{28}H_{31}O_6N$	209–211	– 21	1956	Colchicum speciosum [9]
Cornigerine	$C_{21}H_{21}O_6N$	268–270	–150	1962	Colchicum cornigerum [15]
N-Methylcolchamine, CC-5	$C_{22}H_{27}O_5N$	208–212	–104	1962	Colchicum cornigerum [15]
6-Hydroxycolchicine, CC-12	$C_{22}H_{25}O_7N$	197–199	– 45	1963	″ [16]
3-Demethylcolchamine, CC-7	$C_{20}H_{23}O_5N$	220–222	– 128	1963	″ [16]
3-Demethyl-N-formyldeacetylcolchicine, S_3	$C_{20}H_{21}O_6N$	230–231	–210	1967	Gloriosa superba [38]
N-Formylcolchamine, CC-19	$C_{22}H_{25}O_6N$	187–188	–202	1969	Colchicum cornigerum [26]
3-Demethylcolchicenine, L-5	$C_{20}H_{21}O_6N$	179–183 (amorph.)	—	1970	Colchicum luteum [30]
Deacetylcolchicine, M-1	$C_{20}H_{23}O_5N$	Amorph.	- 146	1972	Merendera robusta [33]
Deacetylcolchiceine, M-2	$C_{19}H_{21}O_5N$	155–157	–185	1972	″ [33]
2-Demethyl-N-formyldeacetylcolchicine	$C_{20}H_{21}O_6N$	Amorph.	—	1975	Gloriosa superba [39]
2,3-Didemethyldeacetylcolchicine	$C_{18}H_{19}O_5N$	Amorph.	—	1975	″ [39]
10,11-Epoxycolchicine	$C_{22}H_{25}O_7N$	251–253	–237	1976	Colchicum latifolium [37]
Colchiciline	$C_{22}H_{25}O_7N$	170–171	–121	1976	″ [37]
Alkaloid CL-1	$C_{22}H_{25}O_7N$	—	—	1976	″ [37]
2-Demethylcolchiciline	$C_{21}H_{23}O_7N$	Amorph.	—	1976	″ [37]

ily Liliaceae. In the USSR they grow mainly in the Caucasus and in Central Asia. The first genus is represented by 12 species and the second by eight. The genus Bulbocodium L. (meadow saffron) is represented by only one species [56].

One of the species of autumn crocus – C. speciosum Stev. – grows abundantly in the northern Caucasus and differs from the other by containing mainly two important tropolone alkaloids – colchicine and colchamine [24]. This plant is also characterized by its very large size. Its corms form the raw material for the production of colchamine, which is used in the chemotherapy of certain diseases [65-68].

From colchicine-containing species of plants more than 90 alkaloids have been isolated, 26 of them with the tropolone ring (Table 1). The structures of 24 compounds have been determined (Table 2).

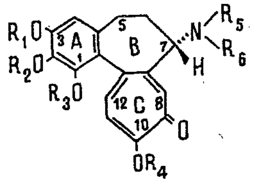
The most widespread alkaloids and those forming the main components in mixtures of tropolone alkaloids are colchicine and colchamine.

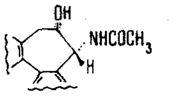
The solubility, crystallization (crystal solvates), and characteristic color reactions of colchicine have been given in the literature [74, 75]. The structure of this compound was established by the efforts of a whole series of workers. Investigations in this direction, which were begun in 1883 by Zeisel, were definitely completed only after 1950 by x-ray structural analysis [76] and the complete synthesis of the alkaloid [77, 78]. Reviews on the establishment of the structure of colchicine have been given in a number of publications [1, 74, 75, 79]. The other alkaloids were discovered and isolated after the complete structure of colchicine had been established, and therefore their study amounted mainly to determining the nature and positions of the functional groups in their tricyclic system.

Colchicine (I) and its natural analogs (see Table 2) consist of three condensed nuclei with various functional groups: an aromatic six-membered ring with free or alkylated hydroxy groups (ring A), a cycloheptadien ring with an acetamido, amino, or alkylamino group (ring B), and an aromatic seven-membered ring with carbonyl and methoxy (rarely hydroxy) groups (the tropolone ring C).

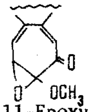
In the known tropolone alkaloids (apart from cornigerine) the C_1 position of ring A is substituted by a methoxy group. At the same time, only recently has a compound been isolated with two hydroxy groups in ring A (2,3-didemethyldeacetylcolchicine) and an epoxy group in ring C (10,11-epoxycolchicine).

TABLE 2

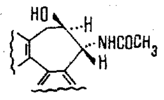
Alkaloid							Reference
	R_1	R_2	R_3	R_4	R_5	R_6	
Colchicine (I)	CH_3	CH_3	CH_3	CH_3	H	$COCH_3$	1,74,75
N-Formyldeacetylcolchicine	CH_3	CH_3	CH_3	CH_3	H	CHO	57
3-Demethylcolchicine	H	CH_3	CH_3	CH_3	H	$COCH_3$	197
Colchamine	CH_3	CH_3	CH_3	CH_3	H	CH_3	100, 107, 165, 175
2-Demethylcolchicine	CH_3	H	CH_3	CH_3	H	$COCH_3$	197
2-Demethylcolchamine	CH_3	H	CH_3	CH_3	H	CH_3	69
Colchicoside	$C_6H_{11}O_5$	CH_3	CH_3	CH_3	H	$COCH_3$	70,193
Colchiceine	CH_3	CH_3	CH_3	H	H	$COCH_3$	1,74,75
3-Demethyl-N-deacetylcolchicine	H	CH_3	CH_3	CH_3	H	H	212
Colchameine	CH_3	CH_3	CH_3	H	H	CH_3	69,165
Speciosine	CH_3	CH_3	CH_3	H	CH_3	$CH_2C_6H_4OH$	71,73
Cornigerine	CH_3	$-CH_2-$		CH_3	H	$COCH_3$	72
N-Methylcolchamine	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3	16,165
3-Demethylcolchamine	H	CH_3	CH_3	CH_3	H	CH_3	16
3-Demethyl-N-formyldeacetylcolchicine	H	CH_3	CH_3	CH_3	H	CHO	38
N-Formylcolchamine	CH_3	CH_3	CH_3	CH_3	CH_3	CHO	26
3-Demethylcolchiceine	H	CH_3	CH_3	H	H	$COCH_3$	30
Deacetylcolchicine	CH_3	CH_3	CH_3	CH_3	H	H	1,33
Deacetylcolchiceine	CH_3	CH_3	CH_3	H	H	H	1,33
2-Demethyl-N-formyldeacetylcolchicine	CH_3	H	CH_3	CH_3	H	CHO	39
2,3-Didemethyldeacetylcolchicine	H	H	CH_3	CH_3	H	H	39



6-Hydroxycolchicine (214)



10,11-Epoxycolchicine (37a)

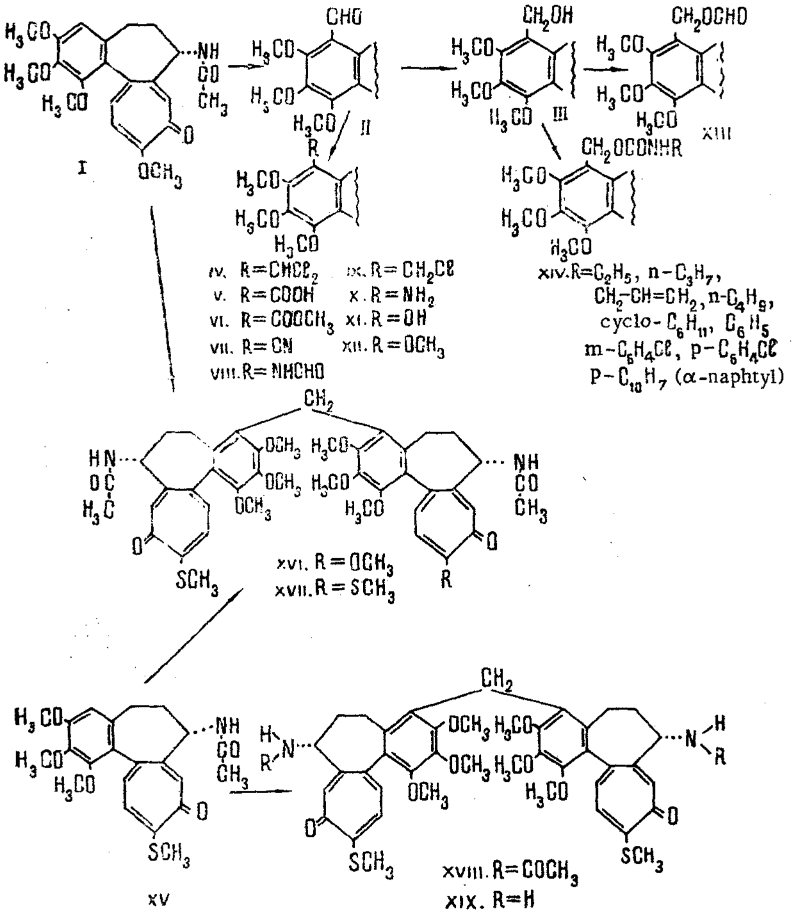


Colchiciline (6β-hydroxycolchicine) (37a)

In view of the fact that colchicine is the most accessible alkaloid of autumn crocuses and botanically related plants, the properties of the tropolone alkaloid are considered mainly in relation to this compound. Colchicine, its tropolone associates, and their photochemical isomers belong to the series of acyclic alkaloids. The presence in many of them of a N-acetyl or N-formyl group imparts a very feeble basic nature to them. At the same time, compounds containing a primary or secondary amino group possess stronger basic properties.

Numerous transformations of colchicine and some of its tropolone associates have been performed. Below we consider the reactions of them that involve the aromatic, cyclopentadiene, and tropolone rings or the whole tricyclic system.

The Aromatic Ring (A). In addition to reactions involving the acylation and alkylation of the hydroxy group in the phenolic compounds, the tropolone alkaloids may also react as a result of the mobility of the hydrogen in the C_4 position. The saturation of the aromatic ring of these compounds by oxygen-containing functional groups increases the mobility of this hydrogen atom and creates favorable conditions for electrophilic attack. However, the instability of the tropolone ring with respect to various reagents does not permit C_4 derivatives to be obtained by their direct action. C_4-Substituted compounds are obtained by the previous formylation of the alkaloids with di(chloromethyl) ether in the presence of stannic chloride or aluminum chloride [80-84]. The introduction of the reactive aldehyde group into the molecule, without affecting the tropolone ring, enables the following C_4 derivatives of colchicine (I) to be obtained. Starting from 4-formylcolchicine (II, Scheme 1), the synthesis has been effected of 4-hydroxymethylcolchicine (III) [81, 85], 4-dichloromethylcolchicine (IV) [81, 84], 4-carboxycolchicine (V) [81, 86], 4-methoxycarbonylcolchicine (VI) [86], 4-cyanocolchicine (VII) [81, 87], and 4-formamidocolchicine (VIII) [88].



Scheme 1

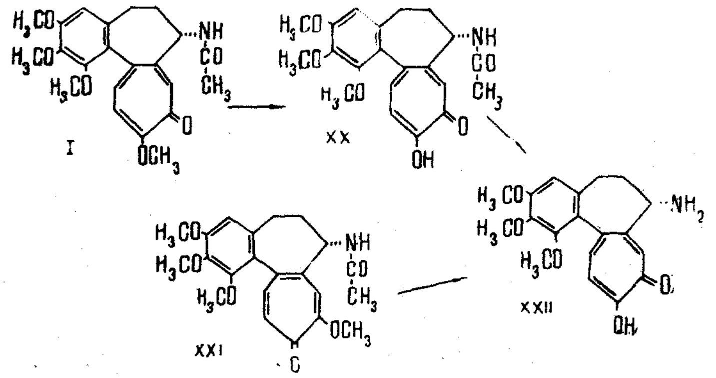
4-Chloromethylcolchicine (IX) [89] and the 4-amino, 4-hydroxy, and 4-methoxy derivatives (X-XII) [91-93] have been isolated in a somewhat different manner.

Starting from 4-hydroxymethylcolchicine, some of its esters have been synthesized – 4-formyloxymethylcolchicine (XIII) [93] and alkyl and aryl isocyanates (XIV) [94].

C_4-Substituted compounds have also been obtained from amino and thio derivatives of colchicine – aminocolchicine [81, 90], methylaminocolchicine [81, 92, 95], dimethylaminocolchicine [81], thiocolchicine (XV) [81, 83, 84, 86-90, 96-99], di(colchicin-4-yl)methane (XVI) [89, 96], colchicin-4-ylthiocolchicin-4'-ylmethane (XVII) [96], di(thiocolchicin-4-yl)methane (XVIII) [89, 96], and bis(N-deacetylthiocolchicin-4-yl)methane (XIX) [96].

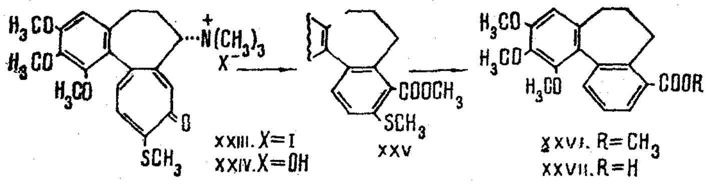
The cycloheptadiene ring (B) of the colchicine alkaloids, as already mentioned, contains a free, methylated, or acetylated amino group. Accordingly it can undergo alkylation, acylation, or deacylation reactions or the elimination of the amino group as a whole. In dilute acids [101-103] and alkaloids [102] the methoxy group of the tropolone ring of colchicine is readily hydroylzed with the formation of colchiceine (XX, Scheme 2). Colchiceine is also formed by the acid hydrolysis of isocolchicine (XXI) [103, 104]. Under more severe conditions or when the reaction is prolonged, colchiceine is converted into deacetylcolchiceine (trimethylcolchicinic acid, XXII) [102, 105, 106]. (See Scheme 2 on following page).

The amide hydrogen in colchicine and other N-acylated alkaloids is completely inert and is not replaced by alkyl or acyl groups. Compounds containing amino and methylamino groups are readily alkylated and acylated, and therefore N-methylcolchicine can be obtained only by the acetylation of colchamine [100, 107].



Scheme 2

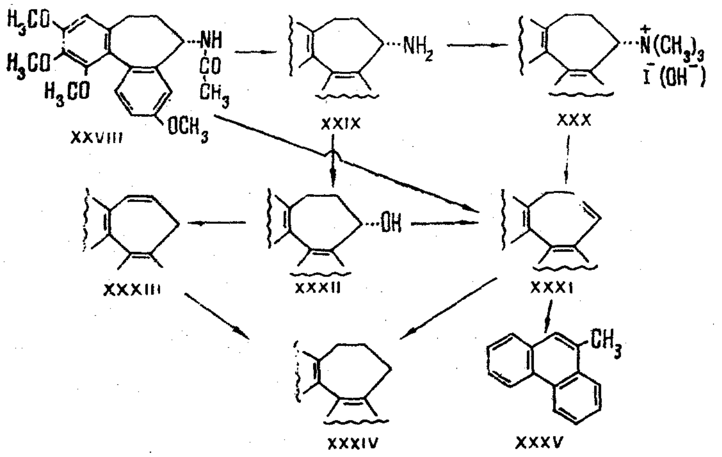
The reactions of the colchicine alkaloids with aklyl iodides take place differently according to the substituting groups on the nitrogen atom. Compounds with a N-acetyl or a N-formyl group do not form methiodides, but those with a primary amino group form them through the hydriodides of the N-methyl derivatives.



Scheme 3

The Hofmann degradation has been performed of the methiodide of N-deacetylthiocolchicine (XXIII, Scheme 3) [108] and of the methiodide of the methyl ether of colchinol (XXX, Scheme 4) [109] and some of its analogs [110]. In this way, (XXX) yielded the methyl ether of deaminocolchinol (XXXI).

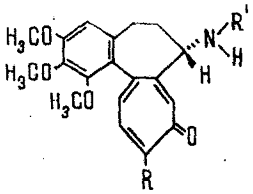
On the Hofmann degradation of (XXIII), its tropolone ring rearranges into a benzene ring and compound (XXV) is formed. The hydrogenation of this substance in the presence of Raney nickel leads to the splitting out of the methylthio group and the formation of compound (XXVI), which is hydrolyzed to the carboxylic acid (XXVII).



Scheme 4

In some colchicine derivatives the elimination of an acetamide or amino group takes place through a stage of the formation of a methiodide. The action of phosphorus pentoxide on the methyl ether of N-acetylcolchinol (XXVIII, Scheme 4) splits out its acetamide group with the formation of the methyl ether of deaminocolchinol (XXXI) [111]. Hydrolysis of the N-acetyl group of (XXVIII) with acid leads to the methyl ether of colchinol (XXIX) [146], which, after the diazotization reaction, is converted into the carbinol (XXXII) [213].

TABLE 3

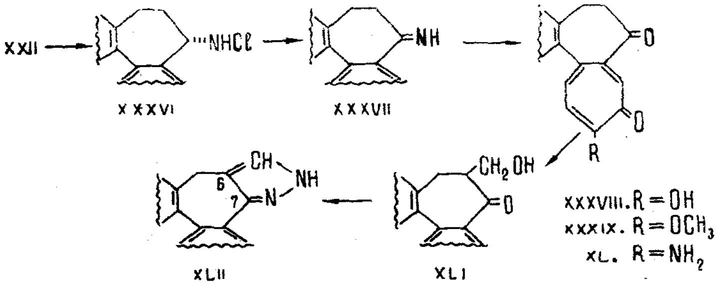


Compound	R	R'	References	Compound	R	R'	References
XLIII	OCH_3	$COCH_2CH_3$	118—120	LI	SCH_3	$CSNHC_6H_5$	126
		$CO(CH_2)_2CH_3$	118,119			$CSNHC_6H_{11}$	
		$CO(CH_2)_4CH_3$					
		COC_6H_5	120			$CSNHC_6H_{12}$	
XLIV	SCH_3	$CO(CH_2)_nCH_3$	121			$CSNHC_{10}H_7$	
		$n=7-10$				(α-naphthyl)	
		$COC_6H_2(OCH_3)_3$	121,122			$CSNHC_{10}H_7$	
		$COC_6H_4NHCOCH_3$	123			(β-naphthyl)	
XLV	OCH_3	$COCH_2X$	124,125			$CSNHCH_2CH=CH_2$	126,127
		X=Cl, Br, F, J		LII	SCH_3	$CONHC_6H_{11}O_5$	128
						(β-D-glucopyranosyl)	
XLVI	OH	$COCH_2X$	124	LIII	SCH_3	$CONHC_6H_7O(OCOCH_3)_4$	128
		X=Cl, Br, F				(β-D-glucopyranosyl)	
XLVII	SCH_3	$COCH_2X$	124,125	LIV	SCH_3	$CSNHC_5H_6O(OCOCH_3)_3$	129
		X=Cl, Br, F, J				(β-D-arabinopyranosyl)	
XLVIII	$N(SCH_3)_2$	$COCH_2X$	124,125			$CSNHC_5H_8O(OCOCH_3)_3$	
		X=Cl, Br, F, J				(α-L-arabinopyranosyl)	
XLIX	OH	$COCHCl_2$	124			$CSNC_6H_7O(OCOCH_3)_4$	
		$COCH_2CH_2Cl$				(β-D-glucopyranosyl)	
		$COCF_3$		LV	SCH_3	$COCH_2CH_2COOH$	130
L	SCH_3	$CONHC_6H_5$	126			$COCH_2CH_2CH_2COOH$	
		$CONHC_9H_{19}$				$COCH=CHCH_2COOH$	
		$CONHC_{10}H_7$		LVI		Gly, Gal, Rib,	131,132
		(α-naphthyl)				Xyl, Ara, Lyx	

The latter, on dehydration with phosphorus pentoxide is converted into the methyl ethers of deaminocolchinol and isodeaminocolchinol [(XXXI) and (XXXIII), respectively] [112, 113]. The hydrogenation of (XXXI) over palladium leads to the dehydro derivative (XXXIV) [113]. Distillation of the methyl ether of deaminocolchinol with zinc dust converts it into 6-methylphenanthrene (XXXV) [109], the structure of which has been confirmed by synthesis [114, 115].

The seven-membered nature of ring B in colchicine has been definitely confirmed by syntheses of the methyl ethers of N-acetylcolchinol [116] and of colchinol [117].

The N-acetyl group of colchicine can be replaced by other functional groups. The conversion of deacetylcolchiceine (XXII, Scheme 5) into deacetamide-7-oxocolchicine (XXXIX) has been described [133]; by the action of N-chlorosuccinimide, (XXII) is converted into N-chlorodeacetylcolchiceine (XXXVI) which, on treatment with alkali, forms the imine (XXXVII). On acetic acid, the latter is converted into (XXXVIII), which is methylated by diazomethane to (XXXIX).



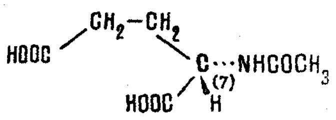
Scheme 5

Under the action of sodium methanolate, the amide of deacetamido-7-oxocolchicine (XL) forms the 6-hydroxymethyl derivative (XLI) which, on reaction with hydrazine hydrate, is converted into C_6, C_7-pyrazolodeacetamidocolchiceine amide (XLII) [134].

Various compounds have been synthesized from N-deacetylated colchicine derivatives: N-acyl (XLIII, XLIV, Table 3), N-haloacetyl (XLV-XLIX), N-alkylcarbamoyl (L), N-alkylthiocarbamoyl (LI), glycopyranosylcarbamoyl (LII), per-O-acetylglycopyranosylcarbamoyl (LIII), per-O-acetylglycopyranosylthiocarbamoyl (LIV), and N-carboxyalkyl (LV) derivatives, N-osides (LVI), and a number of other substances.

The cycloheptadiene ring of the colchicine alkaloids contains an asymmetric arbon atom – C_7 – which explains their optical activity. Natural colchicine is a levorotatory compound. Corrodi and Hardegger [135] have racemized it in alcoholic alkali in the form of benzylidene-N-deacetylcolchiceine and have separated the reaction product with the aid of α-camphorsulfonic acid into optical antipodes. By subsequent acetylation and methylation of the latter they isolated the levo- and dextrorotatory optical isomers of colchicine.

Corrodi and Hardegger [136] have also established the configuration of the substituent at the C_7 atom of colchicine. The vigorous oxidative cleavage of the alkaloid with ozone followed by the oxidation of the ozonization product with performic acid gave them N-acetyl-L-glutamic acid (LVII).



LVII

This amino acid contains the same asymmetric carbon atom as is present in the alkaloid molecule. N-Acetyl-L-glutamic acid is configurationally related to α-glyceraldehyde, and on this basis for colchicine and related compounds the absolute configuration (I) has been suggested (see Table 2).

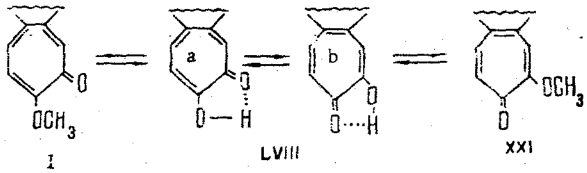
Šantavý et al. [137] have confirmed these authors' results by a study of the optical rotatory dispersion of colchicine and its derivatives.

The confirmation of the amino group of the colchicine alkaloids has been studied by V. V. Kiselev and M. E. Perel'son [138]. On the basis of the presence of a trans-diaxial coupling constant in the PMR spectrum, these authors concluded that the proton at C_7 was axial and, consequently, the amino group was equatorial.

The Tropolone Ring C. The reactions taking place with a change in the substituents in this seven-membered ring or transformations of the ring itself mainly determine the specific properties of the colchicine alkaloids. Like other tropolone compounds, these alkaloids are capable of forming salts in view of the basic properties of the tropolone system [139-141]. Consequently, the colchicine alkaloids with basic properties form dihydrochlorides and other analogous salts.

The carbonyl group of the tropolone alkaloids does not form functional derivatives, while the methoxy group is very mobile and is readily saponified or replaced by other functional groups. These properties and the ease of hydrolysis under the action of acid and alkalis are due to an enhancement of the acidic properties of the tropolone hydroxyl under the influence of the neighboring carbonyl group. The tropolone hydroxy group possesses the properties that are characteristic of phenols and enols.

Characteristic of the free, nonesterified, tropolone system are two tautomeric forms – (LVIIIa) and (LVIIIb) (Scheme 6) [139-141]. The methylation of unsymmetrically substituted tropolones such as colchiceine with diazomethane correspondingly forms a mixture of two isomeric methyl ethers. One of them belongs to the n series – to the colchicine (I) series – and the other to the iso series – the isocolchicine (XXI) series [103, 104, 142]. Similarly, on methylation, deacetylcolchiceine forms deacetylcolchicine and deacetylisocolchicine [143], and colchameine gives colchamine and isocolchamine [107].



Scheme 6

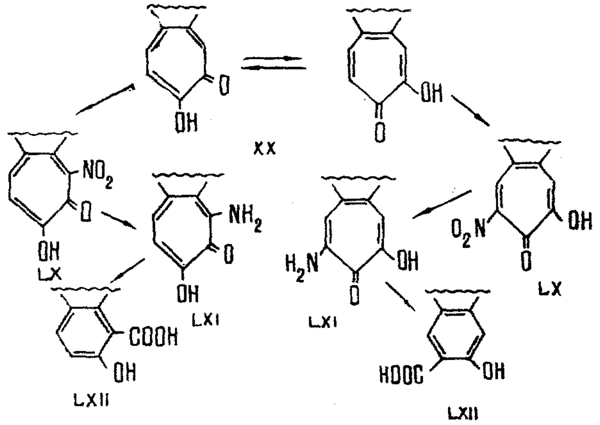
The action of other diazoalkanes on colchiceine gives its ethyl, propyl, allyl, and butyl ethers [57, 118, 120]. The alkylation of colchiceine with diethyl sulfate in an alkaline medium leads to the ethyl ethers of colchiceine and of isocolchiceine [104].

The tropolone hydroxyl of colchiceine is also alkylated by alcohols in the presence of hydrogen chloride, but with a low yield of the ethers [106, 109, 144]. In ethanolic solution in the presence of p-toluenesulfonic acid, colchicine undergoes a transesterification reaction giving as the main product the ethyl ether of colchiceine with a small amount of the ethyl ether of isocolchiceine as impurity [104]. In spite of its acidic nature, colchiceine also undergoes acetylation and benzoylation [120, 145, 146].

In aqueous and ethanolic solutions, tropolone alkaloids with a free hydroxy group (colchiceine and analogs) give an emerald green coloration with ferric chloride. The color of the solution does not change on acidification. Where the hydroxy group is methylated, it is previously hydrolyzed under the action of mineral acids. This color reaction, known as the Oberlin–Zeisel reaction [1, 101, 102], is one of the most important reactions for detecting the presence of colchicine alkaloids.

Of the specific transformations of colchicine alkaloids due to the presence of the tropolone ring, most interest is presented by substitution and rearrangement reactions.

Substitution reactions in tropolone compounds may be both electrophilic and nucleophilic. Electrophilic substitution reactions have been fairly well studied in relation to simple tropolone derivatives but have scarcely been investigated at all for the colchicine alkaloids, with the exception of the nitration of colchiceine (XX, Scheme 7) in acetic acid [147]. The nitration of (XX) gives a mononitro derivative which can be reduced catalytically to an amphoteric amino derivative. Diazotization of the latter leads to a rearrangement of the tropolone ring and to the formation of a hydroxy carboxylic acid. Because of tautomerism in the tropolone ring of the alkaloid these transformations can be illustrated by two schemes and the derivatives, respectively, by structures (LX)–(LXII).



Scheme 7

Nucleophilic substitution reactions of tropolone alkaloids have been studied in fairly great detail. The action of various anionoid reagents on colchicine has given a large number of amino, alkylamino, acylamino (LXIII, Scheme 8), dialkylamino (LXIV), and alkylthio derivatives (LXV). (See Scheme 8 following page).

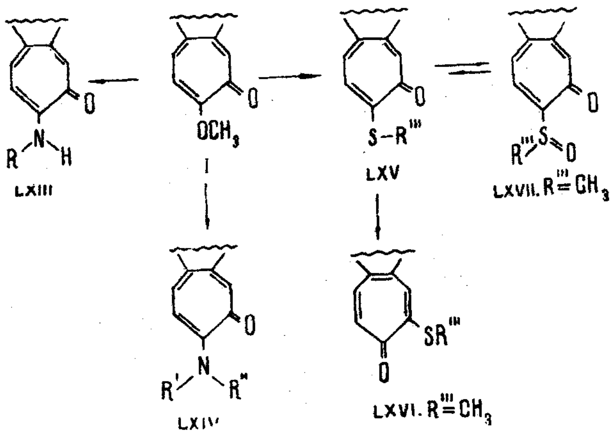
Dicolchicidyl-L-lysine [161], colchicidylglycylglycine, and colchicidylglycyl-D-valine [156] have also been obtained.

Reactions forming amino derivatives are performed in ethanolic and aqueous solutions by the action of ammonia or various amines and their derivatives. Thioalkyl derivatives are obtained by the action on colchicine of alkyl mercaptans in the presence of p-toluenesulfonic acid or zinc choride.

Amino derivatives of colchiceine (colchicine) are known, such as colcichine(alkyl)amides [151, 162], colchiceine(alkyl)amides [102, 150, 158, 163, 164], (alkyl)aminocolchiceines [149], (N-alkyl)colchicamides [119, 16 tropaminones [167-169], and (alkyl)colchaminones [170].

The hydrolysis of thiocolchicine with dilute acid leads to a mixture of deacetylthiocolchicine and deacetyl isothiocolchicine (4%). Acetylation of the latter with acetic anhydride gives isothiocolchicine (LXVI) [171].

The action of methyl mercaptan on isocolchicine in the presence of p-toluenesulfonic acid also forms thi colchicine [159]. The reaction of isocolchicine with methyl mercaptan leads to a mixture of pseudothiocolchicine and isothiocolchicine [171]. The N- and S-alkyl groups of these compounds, unlike methoxyl in a tropolone ring, are stable to acid hydrolysis. By the action of dilute acids on amino and thio derivatives of the



Scheme 8

LXIII. R=H [102, 104, 148–150], CH_3 [148–152], C_2H_5, C_3H_7 [148, 150–152], $CH_2CH{=}CH_2$, $CH(CH_3)_2$, $CH_2CH_2NH_2$ [151, 152], $CH_2CH_2OC_2H_5$ [151], C_4H_9 [148, 150], C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}, CH_2CH_2Cl [150], $CH_2C_6H_5$ [149, 152], $CH(CH_2C_6H_5)CH_3$ [152], $COOC_2H_5$ [149], CH_2CH_2OH [149, 150], CH_2COOH, CH_2CH_2COOH [153], $CH(COOH)CH_2CH_2COOH$ [154], $(CH_3)_2$-$CH(NH_2)COOH$, $(CH_2)_4CH(NH_2)COOH$, $HC(COOH)(CH_2)_3$-$NHC({=}NH)NH_2$ [155, 156], $(CH_2)_2N(C_2H_5)_2$, $(CH_2)_3N(CH_3)_2$, $(CH_2)_3N(C_2H_5)_2$ [157], $C_3H_3N_2 \cdot C_2H_4$ (histamine) [152].

LXIV. $R^I = R^{II} = CH_3$ [150–152, 158], C_2H_5 [149, 150, 152], CH_2CH_2OH [150]. $R^I = CH_3$; $R^{II} = C_3H_7$ [152], $R^I + R^{II} = C_5H_{10}$ ( ) [152].

LXV. $R^{III} = CH_3$, C_2H_5, $CH_2C_6H_5$ [159, 160].

tropolone alkaloids it is possible to obtain deacetylated reaction products preserving the substituents in ring C without change [106, 154, 156, 159, 160, 172-174]. However, in alkaline solutions colchiceine amides hydrolyze to colchiceine [102, 104, 120]. An alkylthio group, like a methoxy group, is capable of being replaced by an amino group [173].

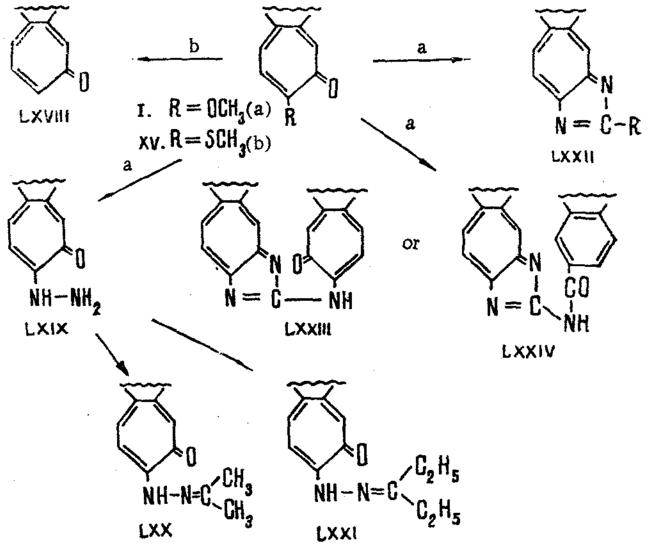
Thiocolchicine is oxidized by monoperphthalic acid to two isomeric S-oxides (LXVII, Scheme 8), in which the isomerism is due to the presence of an asymmetric S atom. These oxides are reduced by sodium bisulfite to the initial thiocolchicine [172]. The reduction of thiocolchicine (XV) in the presence of Raney nickel gives colchicide (demethoxycolchicine, LXVIII) [173]. On the basis of this compound, it has become customary to call amino and thio derivatives of the tropolone alkaloids aminocolchicides and thiocolchicides, respectively [173-175].

With hydrazine hydrate, colchicine forms compound (LXIX) (Scheme 9), which, on condensation with acetone and with methyl ethyl ketone, gives the crystalline products (LXX) and (LXXI) [176]. (See Scheme 9, following page).

The reaction of colchicine with guanidine leads to two imidazole derivatives – aminocolchimadazole (LXXII, R = NH_2) and colchimidazolylcolchaminone (LXXIII) or colchamidazolylcolchicamide (LXXIV) [176, 177] – and the reaction with thiourea leads to thiocolchimidazole (LXXII, R = SH) [176].

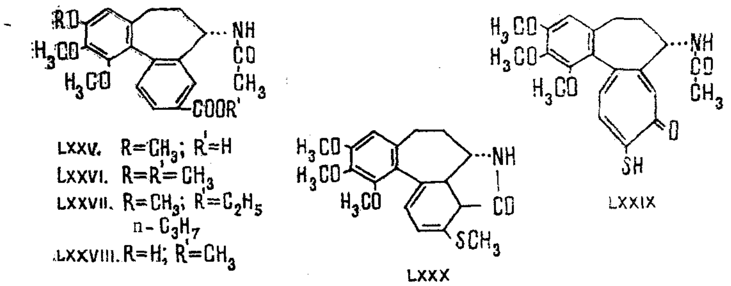
Reactions involving the rearrangement of the tropolone ring of the colchicine alkaloids take place under the action of various reagents – aqueous solution of alkalis [178], alcoholates [149, 178, 179], hydrogen peroxide [180], hypoiodite [146, 181, 182], hypobromite [146, 183], sodium methyl sulfide [176], and some other compounds. As a rule, the reaction is performed in an alkaline medium and leads to hydroxy and carboxy derivatives of benzene.

On brief heating in methanol solution with a catalytic amount of sodium methanolate, colchicine is converted into methyl colchicinate (allocolchicine, LXXVI) [104, 149, 178, 179, 184, 185]. The use of alcoholates of other alcohols in this reaction gives the corresponding esters of colchicinic acid (allocolchiciene, LXXVII)



Scheme 9

[149, 179]. However, in the majority of cases, instead of the expected ester, the carboxylic acid (allocolchiceine, LXXV) is isolated, the ester formed being hydrolyzed in an alkaline aqueous medium.



LXXV. $R=CH_3$; $R'=H$
LXXVI. $R=R'=CH_3$
LXXVII. $R=CH_3$; $R'=C_2H_5$, $n\text{-}C_3H_7$
LXXVIII. $R=H$; $R'=CH_3$
LXXX
LXXIX

As a result of a rearrangement of ring C under the action of an alcoholate, isocolchicine [104, 170], thiocolchicine [159, 171], and isothiocolchicine and pseudothiocolchicine [171] are also converted into allocolchiceine. On methylation with diazomethane, allocolchiceine forms allocolchicine [178-180].

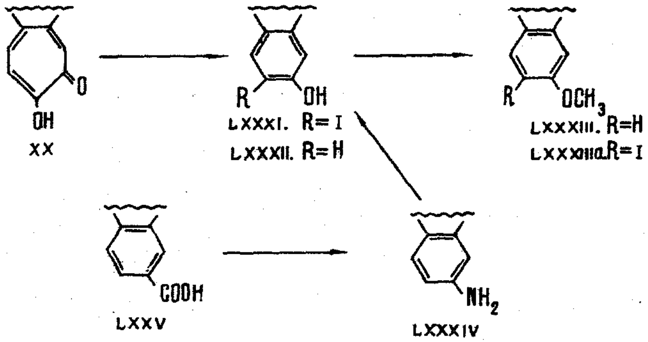
Analogs of allocolchicine and allocolchiceine are also obtained from various tropolone associates of colchicine. Two compounds of this series – allocolchicine (LXXVI) and 3-demethylallocolchicine (LXXVIII) – have been isolated from a plant [186].

In the reaction of colchicine with a sodium methyl sulfide no rearrangement of the tropolone ring is observed and thiocolchiceine (LXXIX) is formed which, under the action of diazomethane, is converted into thiocolchicine (methylthiocolchicide) [176]. The action of sodium methyl sulfide on thiocolchicine leads to the formation of a mixture of allocolchiceine and a neutral compound with a γ-lactam grouping (LXXX) [187].

The reaction of colchiceine (XX) with halides in an alkaline medium forms reaction products with the loss of one carbon atom from the tropolone ring, phenol derivatives being formed. Hypoiodite converts (XX) into N-acetyliodocolchinol (Scheme 10, LXXXI), which, on reduction with zinc in acetic acid, is converted into N-acetylcolchinol (LXXXII) [146]. The same substance is formed from colchiceine directly by the action of hydrogen peroxide [180]. (See Scheme 10 following page).

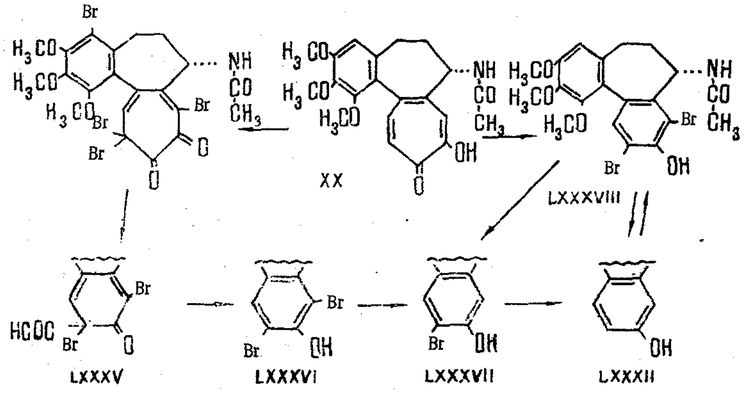
The definitive structure of N-acetylcolchinol was put forward by Cook et al. [112].

N-Acetylcolchinol has also been obtained from allocolchiceine (LXXV): by the Schmidt reaction, (LXXV) is converted into the amide (LXXXIV) which, after diazotization, is converted into (LXXXII) [179]. Under the action of diazomethane or dimethyl sulfate, (LXXXI) and (LXXXII) form the methyl ethers (LXXXIII) [180].



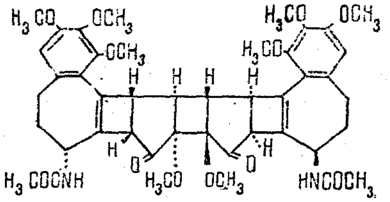
Scheme 10

The action on colchiceine of bromine in acetic acid leads to tribromocolchiceinic acid (LXXXV, Scheme 11) [146, 183]. On being heated in solutions of carbonates, this acid is decarboxylated and is converted into N-acetyltribromocolchinol (LXXXVI) [183]. The latter is reduced by zinc in acetic acid to N-acetylbromocolchinol (LXXXVII) and further by zinc in alkalis to N-acetylcolchinol (LXXXII). The action of bromine on colchiceine and on N-acetylcolchinol in an alkaline medium converts them into N-acetyldibromocolchinol (LXXXVIII). This compound is reduced by zinc in acetic acid to N-acetylbromocolchinol (LXXXVII) and further by zinc in alkaline solution to N-acetylcolchinol (LXXXII).



Scheme 11

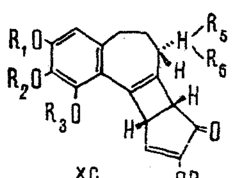
Under the prolonged action of sunlight or on irradiation with UV light, the tropolone alkaloids undergo photochemical isomerization. Three types of photochemical isomers of the tropolone alkaloids are known, being assigned to the α, β, and γ series. A photochemical isomer of the α series is obtained only from colchicine and has the dimeric structure (LXXXIX) [188].



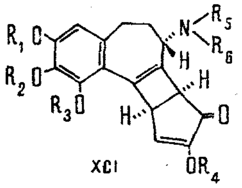
LXXXIX

Photochemical isomers of the β and γ series (XC and XCI, respectively) have been isolated both from plants and by the irradiation of many of the tropolone alkaloids and some of their derivatives [34, 57, 58, 189, 190]. These compounds have been widely discussed by Kuhn et al. [190]. (See Scheme on following page).

Reduction Reactions. The hydrogenation of colchicine in the presence of Adams catalyst leads to a hexahydro derivative (XCII, Scheme 12) [191, 192]. When platinum oxide is used for the reaction, together with

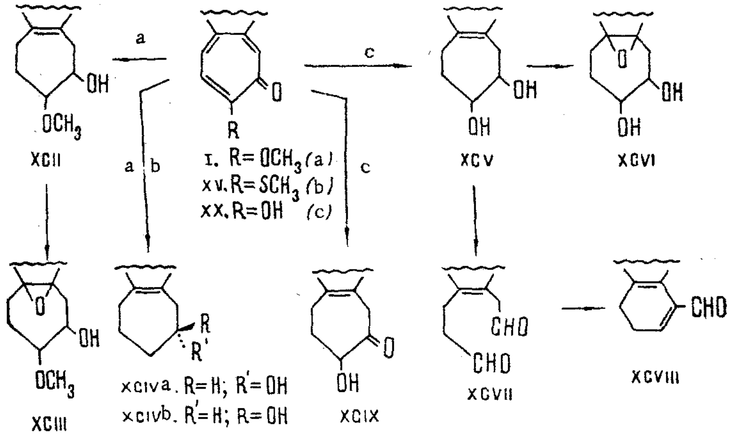


XC



XCI

(XCII) the isomeric demethoxyhexahydrocolchicines (XCIVa and XCIVb) are formed [147, 191, 192]. The latter are also obtained by the hydrogenation of thiocolchicine (XV) in the presence of palladized Raney nickel [172].



Scheme 12

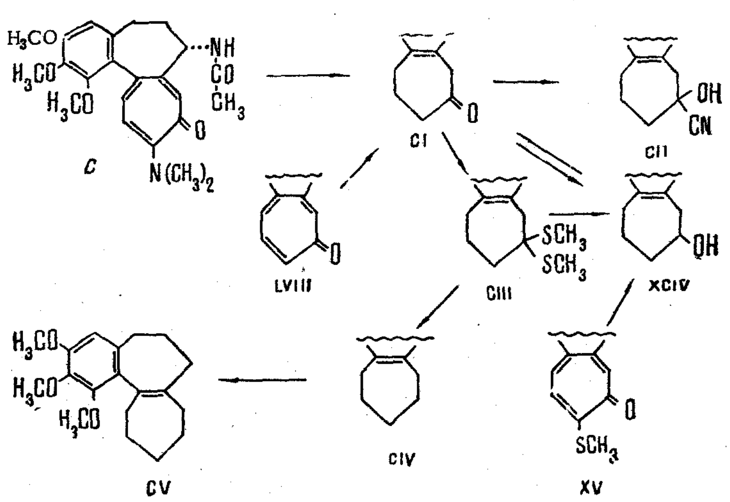
The hydrogenation of colchiceine (XX) over Raney nickel converts it into hexahydrocolchiceine (XCV), which is a diol. Periodate oxidation of the latter forms the dialdehyde (XCVII) which undergoes the aldol condensation and cyclizes to the monoaldehyde (XCVIII). This reaction was one of the most important confirmations of the seven-membered nature of ring C in colchicine [145]. In the presence of a palladium catalyst, colchiceine hydrogenates to a tetrahydro derivative (XCIX) [145].

Thus, in the hydrogenation of the tropolone alkaloids complete saturation of the tropolone ring cannot be achieved, and the hexahydro derivatives obtained retain an ethylenic double bond. Its presence in hexahydrocolchicine and hexahydrocolchiceine has been established by their oxidation with perphthalic and perbenzoic acids to the corresponding epoxy compounds (XCIII, XCVI) [145].

The successive splitting out of the individual functional groups in dimethylaminocolchicide (C, Scheme 13) on hydrogenation by methods excluding rearrangement leads to octahydrodemethoxydeoxydeacetamidocolchicine (CV) [158, 164]. On hydrogenation in the presence of platinum oxide and palladium, dimethylaminocolchicide is converted into tetrahydrodemethoxycolchicine (CI). The reduction of its dithioacetal (CIII) with Raney nickel leads to hexahydrodemethyoxycolchicine (XCIV) and hexahydrodemethoxydeoxycolchicine (CIV). Deamination of the latter with phosphorus pentoxide followed by hydrogenation over platinum oxide and palladium gives (CV). (See Scheme 13 following page).

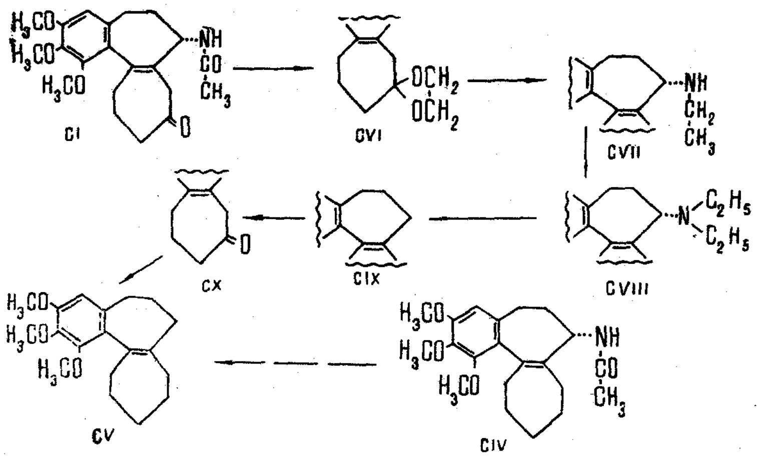
Tetrahydro- and hexahydrodemethoxycolchicines (CI, XCIV) are also obtained by the hydrogenation of colchicine (LVIII) and methylthiocolchicine (XV), respectively [173]. The elimination of the acetamide group from tetrahydrodemethyxycolchicine and from hexahydrodemethoxydeoxycolchicines has also been brought about by some other methods [194].

The reaction of tetrahydrodemethoxycolchicine (CI, Scheme 14) with ethylene glycol gives the ethylene ketal (CVI), which, on reduction with lithium tetrahydroaluminate, forms the deacetyl-N-ethyl derivative (CVII). The N-acetylation and reduction of this compounds lead to the ethylene ketal of N-diethyltetrahydrodemethoxydeacetylcolchicine (CVIII), which, on Hofmann degradation and hydrogenation, is converted into the ethylene ketal of hexahydrodemethoxydeacetamidocolchicine (CIX). Hydrolysis of the ketal liberates the ketone (CX), the



Scheme 13

reduction of the dithioacetal of which in the presence of Raney nickel leads to octahydrodemethoxydeoxydeacetaminocolchicine (CV).



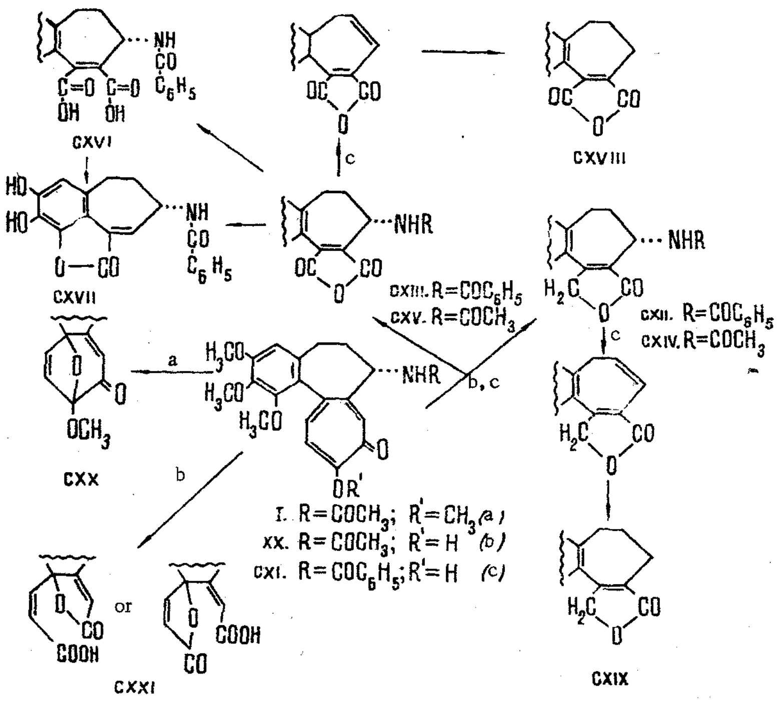
Scheme 14

The deamination of hexahydrodemethoxydeoxycolchicine (CIV, Scheme 14) is effected by a similar method: reduction of a N-acetyl group to a N-ethyl group, the introduction of a new N-acetyl group, followed by reduction and the Hofmann degradation of a quaternary base derivative. Hydrogenation of the deaminated compound has given octahydrodemethoxydeoxydeacetamidocolchicine (CV).

In compound (CV) ring C also retains an ethylenic double bond, which has been confirmed by its oxidation to an epoxy derivative. The structure (CV) for octahydrodemethoxydeoxydeacetamidocolchicine has been confirmed by total synthesis [195].

Oxidation Reactions. Potassium permanganate and ferricyanide oxidize colchicine in an alkaline medium with complete destruction of the tropolone and cycloheptadiene rings and giving 3,4,5-trimethoxyphthalic anhydride [146, 196]. The same compound is obtained by the potassium permanganate oxidation of colchiceine, and N-acetyliodocolchicinol [146]. In phenolic compounds, to determine the position of the hydroxy group their ethyl ethers are oxidized to 2-ethoxy-1,3-dimethoxyphthalic or 3-ethoxy-1,2-dimethoxyphthalic acid [69, 197]. The oxidation of cornigerine leads to isocotarnic acid [72].

On careful oxidation of N-benzoyldeacetylcolchiceine (CX , Scheme 15) with potassium permanganate in the cold, N-benzoylcolchide (CXII) and N-benzoylcolchinic anhydride (CXIII), which has become known as "Windaus's anhydride," are obtained. Under similar conditions, colchiceine (XX) yields N-acetylcolchide (CXIV) [146, 199, 200].



Scheme 15

On being heated in the acetic acid, (CXIII) is converted into N-benzoylcolchinic acid (CXVI). Heating either (CXIII) or (CXVI) with hydriodic acid lead to the lactone (CXVII) [146, 198]. The deamination of (CXII) and (CXIII) with phosphorus pentoxide [199] followed by hydrogenation over palladium in acetic acidic acid converts them into compounds (CXIX) and (CXVIII) [199, 200]. The structure of dihydrodeaminocolchinic anhydride (CXVIII) has been confirmed by synthesis [200, 201].

Potassium dichromate oxidizes colchicine to a compound with an oxygen bridge in the tropolone ring – oxycolchicine (CXX) [202-207]. In the case of chromic acid, far-reaching oxidation takes place with the formation of succinic acid [208]. Sodium periodate oxidizes colchiceine to the unsaturated γ-lactone-carboxylic acid (CXXI) [142, 209].

The far-reaching oxidation of the methyl ether of N-acetyliodocolchinol (LXXXIIIa, Scheme 10) with nitric acid and potassium permanganate degrades it to 4-iodo-5-methoxyphthalic acid. On reduction with zinc in acetic acid, the latter is converted into 5-methoxyphthalic acid [109, 146, 181, 184]. The same acid is obtained from the oxidation of the methyl ether of N-acetylcolchinol.

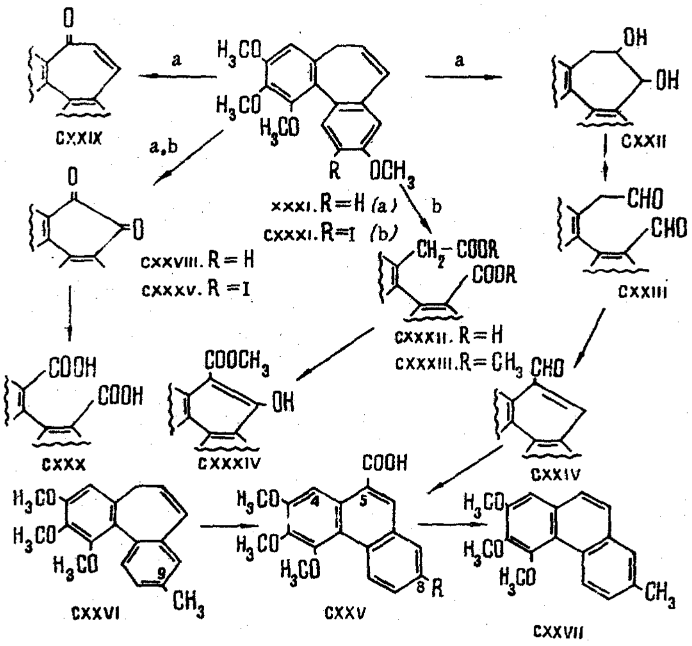
N-Acetyltribromocolchinol (LXXXVI, Scheme 11) is oxidized by potassium permanganate to 3-bromo-4,5,6-trimethoxyphtahlic acid, which confirms the presence of one of the bromine atoms at the C_4 position of the benzene ring. The oxidation of N-acetyldibromocolchinol (LXXXVIII) leads to 3,4,5-trimethoylphthalic acid [183].

When colchicine is fused with alkali and is oxidized with potassium permanganate, trimellitic and terephthalic acids are formed [146]. The oxidation of allocolchiceine with nitric acid and potassium permanganate also leads to trimellitic acid [185, 210].

The monocyclic aromatic acids mentioned above are the main foundations for establishing the first tricyclic structure of colchicine, suggested by Windaus [109].

The methyl ether of deaminocolchinol (XXXI, Scheme 16) is oxidized by osmium tetroxide to the glycol (CXXII), which, under the action of lead tetraacetate, passes into the dialdehyde (CXXIII). This compound is converted by the aldol condensation into 1,2,3,8-tetramethoxyphenanthrene-5-carbaldehyde (CXXIV). The latter, on oxidation by potassium permanganate, gives the carboxylic acid (CXXV, R = OCH_3) [112, 182]. (see Scheme 16 following page).

On oxidation under similar conditions, methyl-9-demethoxydeaminocolchinol (CXXVI) forms 1,2,3-trimethoxy-8-methylphenanthrene-5-carboxylic acid (CXXV, R = CH_3). On being heated in quinoline with copper chromite this acid is decarboxylated to 1,2,3-trimethoxy-8-methylphenanthrene (CXXVII) [110].



Scheme 16

Potassium dichromate oxidizes (XXXI) in acetic acid to 1,2,3,8-tetramethoxyphenanthrene-5,6-quinone (CXXVIII) and the unsaturated ketone (CXXIX) [112]. The further oxidation of (CXXVIII) with hydrogen peroxide converts it into tetramethoxydiphenic acid (CXXX) [211]. The oxidation of the methyl ether of isodeaminocolchinol (XXXIII, Scheme 4) under similar conditions gives 1,2,3,8-tetramethoxyphenanthrene-6-carbaldehyde.

The methyl ether of deaminoiodocolchinol (CXXXI) is oxidized by potassium permanganate in acetone to the dicarboxylic acid (CXXXII), the dimethyl ester of which (CXXXIII) cyclizes under the action of sodium methanolate to the methoxycarbonylphenanthrol (CXXXIV). The action of manganese dioxide on (CXXXI) has yielded phenanthrenequinone (CXXXV) [182].

The substitution, rearrangement, reduction, and oxidation reactions of colchicine and its derivative and' natural analogs that have been considered above have played an important role in the study of their structures. The possibility of varying the different substituting groups in the tricyclic structure of the tropolone alkaloids, the high mobility of the methoxy group of the tropolone ring, and the susceptibility of this ring to transformations create wide possibilities for modifying their molecules. It does not appear possible to cover completely all the transformations and derivatives of colchicines and its tropolone associates in this review. Many of the compounds obtained have been subjected to pharmacological study [1, 119, 215]. A large number of publications has also been devoted to their biogenesis and to spectral methods of investigation.

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